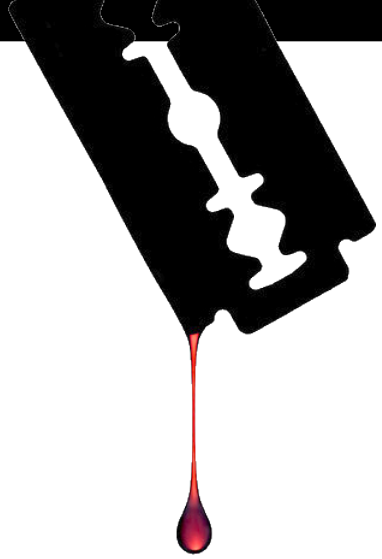

# THE SUICIDE PILL.

A JEFF PRAGER PUBLICATION

... what you don't know
might just make you
kill yourself, or worse,
you might live ...

AND VERY FEW PEOPLE KNOW

RESPECT
SUPPORT YOUR LOCAL
THOUGHT POLICE
Don't speak out or question.
Closed minds STOP thought crimes!
BIG BROTHER IS WATCHING YOU

# THE SUICIDE PILL

# MEFLOQUINE

## THE AGENT ORANGE OF THIS GENERATION

a Jeff Prager publication

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http://www.jeffpragercollections.com

## AN ONGOING GLOBAL COVERUP OF VAST PROPORTIONS

## THE SUICIDE & MURDER DRUG

The drug you're about to read about is no longer prescribed in the United States under its original name and is a "drug of last resort" in the UK. However, the pharmaceutical formula is still prescribed in the USA and UK under a different name. This eBook explains both the history of the civilian, NGO and military complications related to Mefloquine, the "Suicide Pill.

Make no mistake, this is a horror story. The terror and the wealth of propaganda that's surrounded it along with the constant and consistent denials is just another of 1000s of examples of what lengths governments and corporations will go to, to protect profit streams at the expense of lives—but that facade is beginning to crack as retired ranking military medical officers begin to speak out.

For almost 30 years this drug has been prescribed without connecting the severe and deadly psychiatric effects with the use of the drug. As a prophylaxis and because Mefloquine is only taken once a week and generally for short durations, when a civilian has a breakdown a year after using the drug, there's no connection. But when relatively young and apparently healthy military veterans returning from the war theater start killing themselves and their wives in large, unexplainable numbers and as the science advanced—we would recognize Mefloquine poisoning at autopsy by about 2006—someone's got some splainin' to do Spanky. The peer review included here goes back 30 years and shows that the research community has known about and/or suspected Mefloquine as a cause of suicide, homicide and much more for several decades while the media, the government and the pharmaceutical industry continue to spew lies and propaganda. No, Mefloquine does not harm everyone that uses it, at least we believe that. But there are safer alternatives and the harm that Mefloquine does cause, as one medical professional states, is worse than malaria itself, the disease it's intended to prevent.

# A HORROR MOVIE IN A PILL

## DR. DONALD MARKS

Dr. Donald H. Marks is a former associate director of clinical research at Roche. Marks left the company in 1991 to take a directorship position with another company and this is what he has to say regarding Lariam and his former employer, Roche:

"Roche has developed an attitude of not adjusting the information it supplies to physicians and patients about the performance and safety characteristics of their drugs." Marks went on to say that there is "ample reason" to believe Lariam causes suicide. Marks said Lariam can cause "spontaneous neurological activity" and "irritation of certain sensitive areas inside the brain" that could lead to suicidal behavior long after someone stops taking it.

## DR. REMINGTON NEVIN

Dr. Remington Nevin is an epidemiologist and former US Army major. Regarding research on Lariam, Dr. Nevin states, "These figures are consistent with Lariam causing symptoms of mental illness including anxiety and depression, and are also consistent with the known association of these conditions with a strongly increased risk of suicide. As a result of its toxic effects, the drug is quickly becoming the "Agent Orange" of this generation, linked to a growing list of lasting neurological and psychiatric problems including suicide." Dr. Nevin describes Lariam as "a horror movie in a pill."

## DR. ELSPETH RITCHIE

Dr. Ritchie is a former US Army medical doctor and she states that the side effects of Lariam are actually worse than contracting malaria. Dr. Ritchie says that "Aviators are barred from taking Lariam. If Aviators are barred someone who drives a tank and shoots a gun should be precluded too."

## LIEUTENANT COLONEL ASHLEY CROFT

In 2011, Lieutenant Colonel Ashley Croft a senior medical officer who spent more than 25 years serving the MoD in the Royal Army Medical Corp and who is an expert on malaria said, "For the past 12 years I was saying this is potentially a dangerous drug—most people can take it without problems but a few people will experience difficulties and of those a small number will become psychotic and because there are other alternatives that are safer and just as effective we should move to them but my words fell on deaf ears. The problem is that it can make people have psychotic thoughts and therefore act in an irrational manner and potentially a manner that is dangerous to themselves or their colleagues, or civilians." Doxycycline and malarone are safer drugs which are as effective in preventing malaria, according to the retired officer. "Really the only people that get it [Lariam] now are the poor old soldiers and they have no choice."

## US SPECIAL FORCES COMMAND

An order issued in 2011 by the US Special Forces Command states: "medical personnel will immediately cease the prescribing and use of mefloquine for malaria prophylaxis. Hallucinations and psychotic behavior can occur and continue for months or years after mefloquine use; cases of suicidal ideation and suicide have been reported."

• Canadian peacekeepers beat, tortured and shot two local teenagers in Somalia in 1993. Major Barry Armstrong, the military commander of the Somalia surgical unit, in a report dated October that year, stated: "I believe there may be an additional, simple explanation for our difficulties in Somalia: Canadian and American troops may have been impaired by the use of mefloquine."

• In 2000, Lance Corporal Kristian Shelmerdine, in the Parachute Regiment, shot himself in the arm while serving in Sierra Leone. He blamed the accident on the drug, claiming to have had bad dreams and woken up to find himself shot, but was found guilty of 'negligent discharge'.

• In 2002 four US soldiers based at Fort Bragg, North Carolina (three of whom had recently returned from Afghanistan, where troops were prescribed Lariam) killed their wives. Two of the soldiers killed themselves.

• In 2004, a US Army reservist shot and killed himself in Iraq—just weeks before he was due to return home. In a US army report which subsequently emerged, an army psychiatrist stated: "if toxicology reveals the presence of mefloquine, SPC Torres' case should be viewed in light of other suicides suspected to be associated with the drug."

Mefloquine's chemical structure is based on one of the first malaria drugs, quinine, that comes from the bark of South America's Cinchona tree. Here, DoD personnel inspect a shipment of bark, branches and leaf from South America.

***Four US soldiers based at Fort Bragg, North Carolina killed their wives. Two of the soldiers killed themselves.***

FDA APPROVED

"Mefloquine may cause dizziness, balance problems, and ringing in the ears. These symptoms can occur at any time during use and can last for months to years after the drug is stopped or can be permanent."

# THE STORY OF BOB

## FOIA Case Report #8504150

It's always been difficult to tell the difference between insurgents and farmers in Afghanistan. Insurgents look like farmers and farmers look like insurgents. There were insurgents everywhere and Bob was constantly in defensive mode.

Bob didn't join the Army until he was 28, his response to 911, feeling as though he might be able to help prevent another similar attack. He was also being sued for $1.4 million dollars, financially destitute and out of business. His high school friend, Marc Edwards, quoted Bob as saying, "I gotta make something right." Unfortunately, that didn't happen.

At about 12:30am on a pitch black and dead silent Afghan night, Bob left the base and trekked the quarter mile to the village of Alikozai armed with his Heckler & Koch nine-millimeter pistol and his M4 rifle, no body armor. This is rural Afghanistan, no street lights, no lights at all—farmers have no electricity in this part of the country.

Once in Alikozai Bob walked into the homes of two village elders, Sayed Jan and Mohamed Naim. In Jan's house Bob discovered Jan wasn't home but the image of Bob armed to the teeth managed to scare more than a dozen or so women and children sleeping in the home into running across the road to Naim's home.

Before following the sounds of the terrified, screaming women and children across the road, Bob peaked into a room in Jan's home and saw a sleeping farmhand. Bob quickly put a few bullets into the sleeping mans body, closed the door and headed in the direction of the frightened cries. Across the street Bob murdered 16 more innocent victims, burning their bodies when he was done. There were survivors too; Rafiullah, a teenage boy, was shot in both thighs, Parmina, a teenage girl, was

### FDA - Adverse Event Reporting System (FAERS)

#### FOIA Case Report Information

**Case ID: 8504150**

**Case Information:**

**Case Type:** EXPEDITED (15-DAY) **eSub:** Y **HP:** Y **Country:** USA **Outcomes:** OT **(A)NDA/BLA:** 019591 /

**FDA Rcvd Date:** 11-Apr-2012 **Mfr Rcvd Date:** 29-Mar-2012 **Mfr Control #:** US-ROCHE-1054403

**Patient Information:**

**Age:** **Sex:** **Weight:**

**Suspect Products:**

| # | Product Name | Dose/ Frequency | Route | Dosage Text | Indications(s) | Start Date | End Date |
|---|---|---|---|---|---|---|---|
| 1 | LARIAM | | | | PRODUCT USED FOR UNKNOWN INDICATION | | |

| # | Product Name | Interval 1st Dose to Event | DeC | ReC | Lot# | Exp Date | NDC # | MFR/Labeler |
|---|---|---|---|---|---|---|---|---|
| 1 | LARIAM | | | | | | | |

**Event Information:**

| Preferred Term ( MedDRA Version #: 16.0 ) | Start Date | End Date | ReC |
|---|---|---|---|
| HOMICIDE | | | |

**Event/Problem Narrative:**

Initial Information for this Spontaneous case, AER number 1054403, was received on 29/Mar/2012 from a Pharmacist and concerns a patient of unknown demographics who was treated with Mefloquine Hydrochloride (Lariam) for an unknown indication. Medical history included TBI (Traumatic brain injury). No concurrent illnesses were reported. No concomitant medications or past drugs were reported. On an unknown date, the patient started Mefloquine Hydrochloride (dose, form and frequency not reported). On an unknown date the patient who was a soldier in the US Army developed homicidal behavior and led to Homicide killing 17 Afghanis. It was reported that this patient was administered Mefloquine in direct contradiction to US military rules that Mefloquine should not be given to soldiers who had suffered TBI (Traumatic brain injury) due to its propensity to cross blood brain barriers inciting psychotic, homicidal or suicidal behavior. The outcome of Homicide was not Reported. There was insufficient information regarding the therapy ongoing status of Mefloquine Hydrochloride. The reporter did not provide the seriousness criteria of the event of Homicide and its causal relationship with Mefloquine Hydrochloride. The company assessed the event of Homicide as medically significant. No further information was available.

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shot in the chest and the groin, Sadiquallah, a 10-year-old boy, had a bullet blow through his ear and imbed in his skull and Zardana, a 7-year-old girl, was shot in the back of the head. Bob pled guilty to 16 counts of murder and 5 counts of attempted murder and will live out his life in Leavenworth prison, no chance for parole., ever. But Bob may be innocent and the pharmaceutical manufacturer at fault. And that's a war Bob will never win.

"Was I in some kind of trance? I'm still baffled by it," says Bob.

The public was told Bob's 4 deployments resulted in PTSD. That Bob had other mental health issues but the Lariam Bob had taken prior to and after arriving in Afghanistan along with the traumatic brain injury Bob had received tells another story entirely. The author of the FDA FAERS report pictured on the previous page seems to think so too. Bob was given Lariam in direct contradiction to US military rules that Lariam should not be given to people with traumatic brain injuries (TBI), which Bob had. The Kandahar Massacre was more than likely not United States Army Staff Sergeant Robert Bales at all because whoever that was that night, it just wasn't Bob, it was Lariam.

# Eye-witness accounts of Bales' rampage

*Residents of Alkozai, one of two Afghan villages in Kandahar Province that were attacked on March 11, allegedly by Army Sgt. Robert Bales, told a McClatchy reporter what they witnessed that night. Here is their account:*

◀ *Bales*

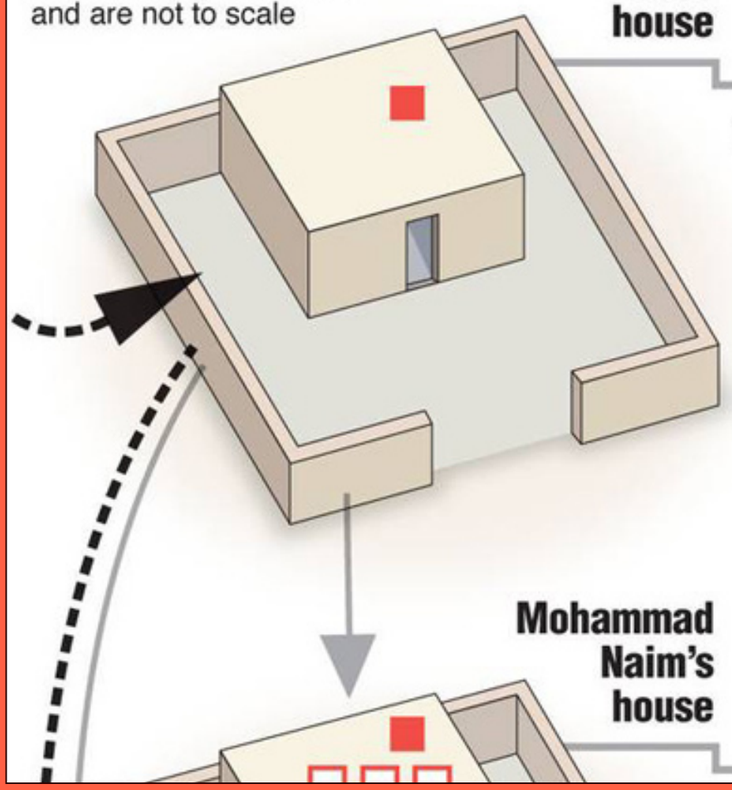
Shooter's movements

Villagers' movements

Dead

Wounded

NOTE: Drawings are schematically simplified and are not to scale




**7** people in the house **2 women, 3 girls; 1 man, 1 boy**

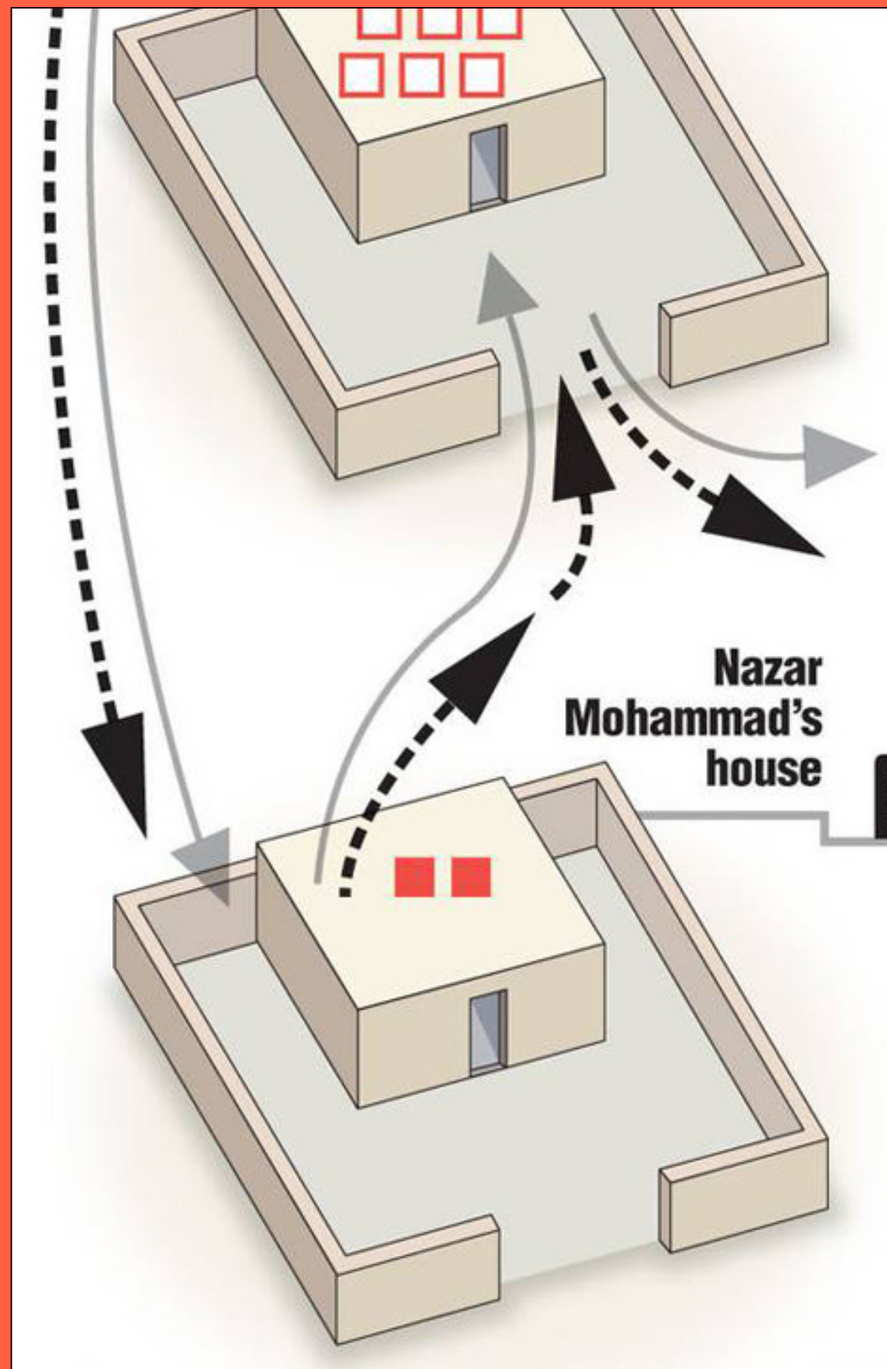
**1.** Fourteen-year-old **Rafiullah** wakes in the middle of the night to the sound of gunfire; sees man moving toward cow shed and shoot family's cow

**Rafiullah** wakes his grandmother **Nikmarghah**; sister **Zardana** (age 7); **Shah Babo**, Rafiullah's great aunt and wife of Nazar Mohammad; and Shah Babo's daughters **Rubbinah** (6) and **Naseema** (5); he tells them to get out of the house

**Khudaidad**, 35-year-old cousin of Sayed Jan, the home owner, is later found dead in guest house; likely the shooter's first victim

*Rafiullah*

**19** people in the house **3 women, 8 girls; 1 man, 7 boys**




2. **Rafiullah**, his grandmother, sister, **Shah Babo** and daughter **Rubbinah** run to house of next-door neighbor, **Haji Mohammad Naim**
3. **Naseema** is chased by shooter to home of her father, **Nazar Mohammad;** shooter enters, shoots dead **Nazar** and **Toraki** (2), daughter of Nazar's second wife, Maryam
4. **Maryam** and **Naseema** flee to **Naim's** house
5. Shooter chases **Maryam** and **Naseema** to Naim's doorstep; shoots, wounds **Naim**

***Naim***

**3** people in the house **1 woman,1 girl; 1 man**

6. **Maryam, Shah Babo** and **Naseema** run to another part of village
7. Shooter enters main room of Naim's house, opens fire; kills **Nikmarghah**, wounds **Rafiullah,** his sister **Zardana,** Naim's son, **Sadiqullah,** and his daughter, **Parmina**, and Shah Babo's older daughter **Rubbinah**
8. Shooter disappears into the night

***Sadiqullah***

**Human toll of Bales' attacks**

- **Alkozai** Four killed; two men, one woman, one girl; six wounded
- **Najiban** 13 killed; two men, three women, two boys, six girls

Lariam® 250 mg Tablets
Mefloquine
250 mg
8 Tablets
The Suicide Drug
Roche

# MATERIAL

# the SUICIDE drug

**Perspectives on Suicide from a Medicolegal Death Investigator who performed over 7,000 forensic autopsies during a 30-year career**

by Joseph Scott Morgan

I still remember the first time I smelled brain. It was my grandfather, cracking open the skulls of squirrels he'd killed. They'd scamper down the sides of pecans and live oaks among the Louisiana timbers where I grew up, enter his sights—then, oblivion. I was very small then, so it never seemed odd when those brains found their way into the scrambled eggs my grandmother would cook up for Papaw. When I was there I'd have some too. The gray matter of tree rats adds a certain sweetness generally absent from an otherwise bland backwoods diet. When I was older, and working in the morgue, the scent would hang in my nostrils for days. Maybe it was the acrid combination of blood and cerebral spinal fluid. The smell of souls. I vividly remember the last time I smelled brain. It was July 2004, and I was peering up at the underside of a Camry. I lay on my back considering the strata of accumulated road filth, spots of tar, and oil coating the wheel wells, tires, and front axle. Wedged among the dark-speckled tapestry were brilliant arrays of pink and gray. They had accumulated in little globs that organically glistened among the machinery. Some hung like stalactites, their tips pointing at my nose. Others were smeared here and there—evidence of something brutal and violent. These particular bits of brain belonged to a 23-month-old child. Earlier that day, his mother had dropped him off at his grandmother's house. As she pulled out of the driveway, the child ran back, perhaps to say goodbye to his momma one last time. She would later recount the slight bump she felt as she turned the wheel and drove away. Obviously she had no idea that bump was her son's skull being crushed between a tire and the outstretched roots of a pine tree. She continued on, unknowingly spraying her son's brains across the underside of her car.

When I arrived on the scene, the paramedics had already shot her up with Ativan. She had been whirling about, slamming her head into the pavement, screaming and tearing at her blouse. In the context of morbidity, one could say that she finally had a true purpose. Bile burned in her throat. Maybe for the first time in a while she felt aware of her flesh, tingling with fear, the nausea causing vomit to rise from her gut.

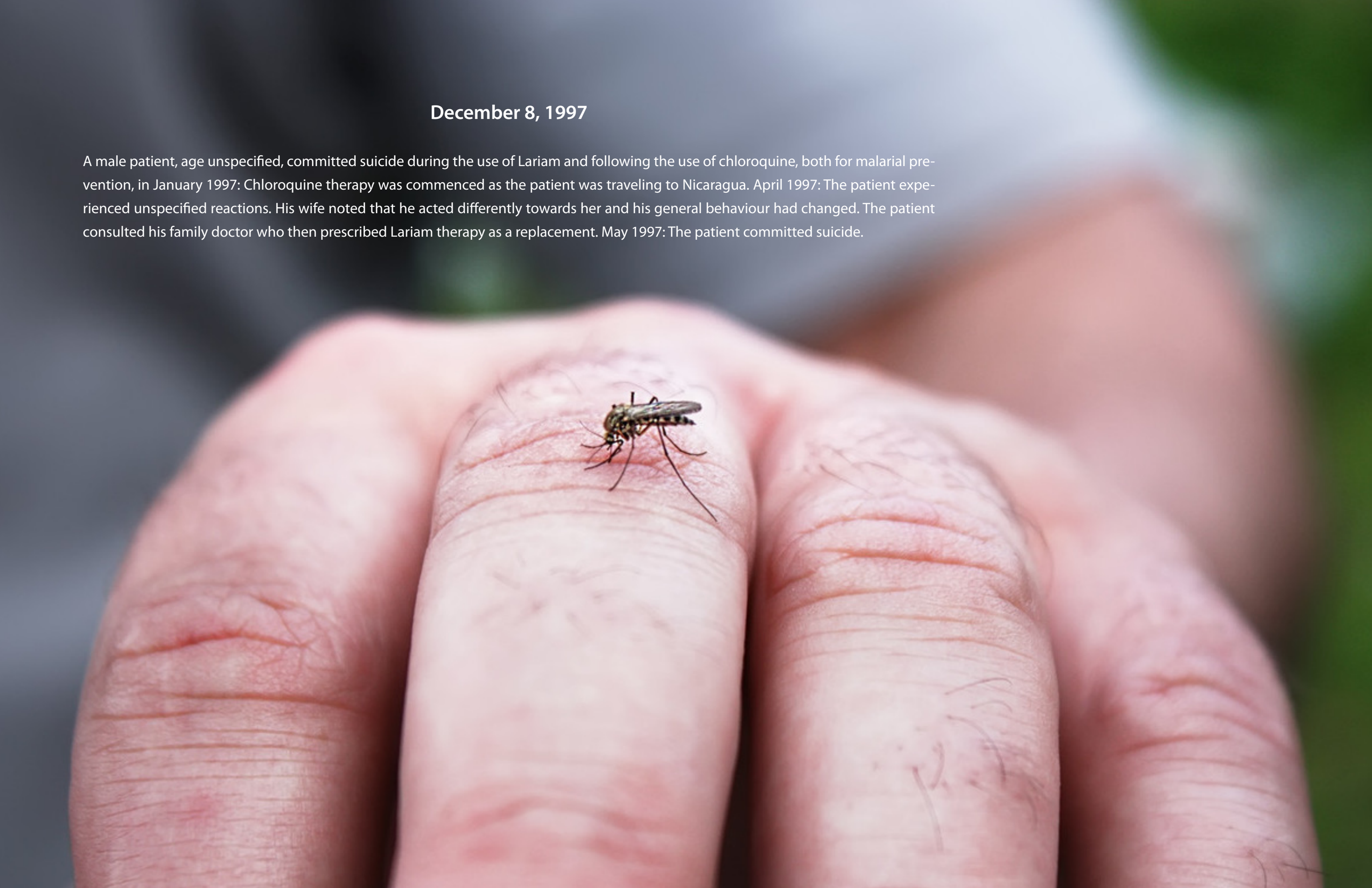
I can tell you from more than 30 years of experience that this is the sort of awakening that death investigators witness daily. It is part of our job to watch humans as they awake from the illusion of happiness, ripped from their mundane existence by the ferocity of death. When this inevitable reality finally punches them in the face, it plunges many of these people into madness.

On my second date with my wife, she quipped, "I never thought about death till I met you." In my view, death is the fart of an old person that's politely ignored. One that most folks don't turn into their profession. For my colleagues and me, death is a siren song. One with crescendos of blood, maggots, trauma, and screams that, for whatever reason, lure us in.

## Just Another Manic Monday

## December 8, 1997

A male patient, age unspecified, committed suicide during the use of Lariam and following the use of chloroquine, both for malarial prevention, in January 1997: Chloroquine therapy was commenced as the patient was traveling to Nicaragua. April 1997: The patient experienced unspecified reactions. His wife noted that he acted differently towards her and his general behaviour had changed. The patient consulted his family doctor who then prescribed Lariam therapy as a replacement. May 1997: The patient committed suicide.



**Feb. 16, 1998**

A 33-year-old male patient committed suicide by hanging following the use of Lariam ... There was no personal or family history of depression or psychological disorder. October 1996: Lariam was started from October 13 through December 21. The patient took his 8th and last dose of Lariam on December 22nd. The patient hanged himself on the 22nd and subsequently died. Police investigation ruled out external influence. The patient had shown no psychological signs.

## June 30, 1998

A 40-year-old male patient committed suicide by hanging himself after using Lariam. He was admitted to a psychiatric ward and was diagnosed with having a fragile personality due to a disturbed childhood, failed marriage and atrocities he witnessed in Africa. He attempted suicide 3 times. The patient committed suicide by hanging himself. The coroner found that the patient had committed suicide whilst the balance of his mind was disturbed. The reporter considered the event possibly related to the suspect drug (Lariam) or the patient's fragile personality/disturbed childhood/failed marriage.

***You are 5 times as likely to commit suicide on Lariam than other anti-Malarial drugs***

## Nov. 10, 2000

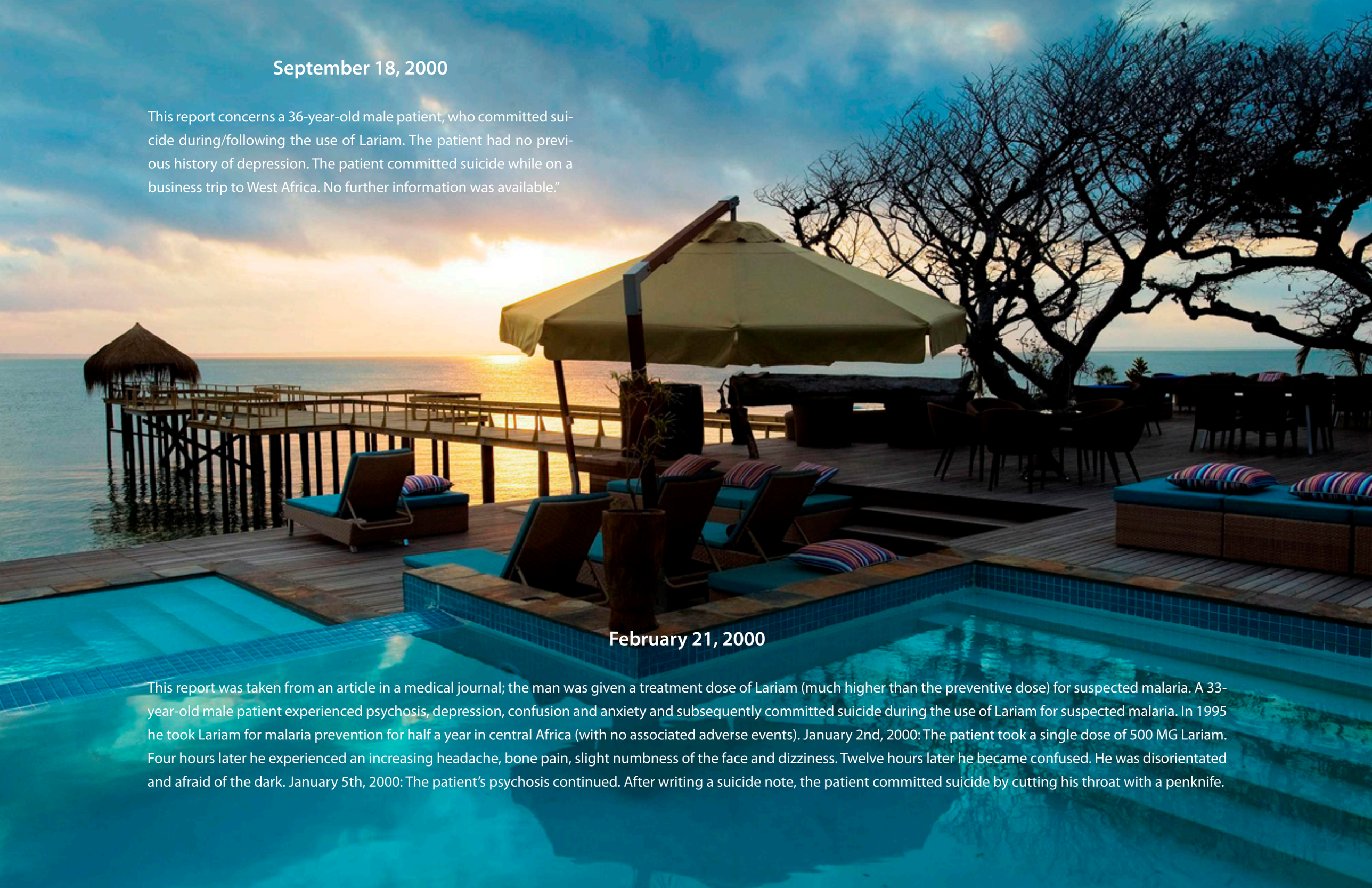
A 20-year-old college student with a history of depression and obsessional thoughts "developed depression, agitation and suicidal thoughts." March 5th, 1991: Depression, nervousness, trembling, agitation, shaking hands. Seen by physician in [deleted] and told the symptoms were due to Lariam. April 12th 1991: Patient attempted suicide with an overdose of Tylenol. Hospitalization for 2 days.

## Oct. 13, 1998

Report of a 29-year-old female patient who experienced medically significant depression and mania and died from committing suicide following the use of Lariam. The patient had no psychiatric history. April 1996: Lariam therapy started. April 1997: The patient developed hypomania (a mild form of mania). Unknown date: She experienced a prolonged depressive episode. Spring 1998: The patient died from committing suicide. The depression had not resolved and the outcome of the mania had not been specified.

## Sept. 4, 1998

A 30-year-old female patient attempted suicide following the use of Lariam for malaria. She also complained of depression, restlessness and insomnia. There is a relevant history of psychosis (brother).



## September 18, 2000

This report concerns a 36-year-old male patient, who committed suicide during/following the use of Lariam. The patient had no previous history of depression. The patient committed suicide while on a business trip to West Africa. No further information was available."

## February 21, 2000

This report was taken from an article in a medical journal; the man was given a treatment dose of Lariam (much higher than the preventive dose) for suspected malaria. A 33-year-old male patient experienced psychosis, depression, confusion and anxiety and subsequently committed suicide during the use of Lariam for suspected malaria. In 1995 he took Lariam for malaria prevention for half a year in central Africa (with no associated adverse events). January 2nd, 2000: The patient took a single dose of 500 MG Lariam. Four hours later he experienced an increasing headache, bone pain, slight numbness of the face and dizziness. Twelve hours later he became confused. He was disorientated and afraid of the dark. January 5th, 2000: The patient's psychosis continued. After writing a suicide note, the patient committed suicide by cutting his throat with a penknife.

**January 13, 2000**

A 23-year-old woman was hospitalized for acute psychosis. The patient had no history of previous psychiatric illness. The patient is a Canadian exchange student in Hong Kong and was going to Cambodia for a three-week vacation. About four hours after her last dose, the patient became totally psychotic. The patient then stole two infant babies in push carts and was taken to the police station. The patient then attempted suicide and jumped off a roof. The patient was taken to a clinic and treated for psychosis. A physician from [deleted] was flown in and escorted her back to [deleted]. The patient was hospitalized again. The patient was still psychotic and experiencing hallucinations. She attempted suicide again by jumping from the seventh floor.

**February 3, 2000**

A 59-year-old female patient made suicide attempts and experienced paranoia following the use of Lariam.The patient (developed) a psychiatric disorder. This consisted of paranoia with evidence of suicidal acts. The person making the report, a health professional, "considered that the psychiatric disorder had been life-threatening and was probably related to the use of Lariam."

## October 5, 2000

A 42-year-old woman was hospitalized due to a suicide attempt after having received Lariam for malaria prevention. She had delirium, anxiety and behavior disturbances—signs of persecution and an urge to run away.

**May 21, 2001**

Although his name is blacked out, this is a report of the suicide of Charles Perry of Bethel, Ohio, who killed himself with a shotgun in January 1999. "A 53-year-old male patient developed obsessive compulsive disorder, delusional disorder (paranoid type), auditory and visual hallucinations, depression, CNS (central nervous system) problems ... cognitive impairment ... delirium, memory loss, agitation, sweating, adjustment disorder, anxiety, insomnia, fatigue ... head pain, abnormal dreams and anorexia during the use of Lariam ... and committed suicide. The patient did not have a history of psychiatric disorders."

Perry's widow, Linda Perry, sued manufacturer Hoffmann La Roche for allegedly failing to warn about the drug's side effects including suicide; Roche denied the charge. The case recently was settled out of court. The terms were not disclosed.

By May of 2002 mounting evidence suggested the anti-malaria drug Lariam—prescribed to Peace Corps volunteers, travelers and U.S. soldiers—had triggered mental problems so severe that in a percentage of users it has led to the ultimate side effect: suicide. Lariam—also known as mefloquine—is a product of Hoffmann-La Roche, the Swiss pharmaceutical company with U.S. headquarters in Nutley, N.J. Lariam has been prescribed to more than 22 million people worldwide since 1985. It was cleared for use in the United States in 1989. Some health experts charge that neither patients nor doctors in the United States are being adequately warned about the risk of suicide from taking Lariam, which is prescribed by U.S. doctors 1,000 times every day. In a two-month investigation reporters found:

- In 1000s of pages of internal documents spanning a decade, the company tracks increasing reports of suicides, suicidal behavior and other mental problems among Lariam users.
- A 1994 Roche safety report notes that because Lariam can cause depression and depression can lead to suicide, "a causal link to Lariam can in theory not be ruled out."
- Dozens of soldiers, Peace Corps volunteers, other government workers and private travelers, in interviews with reporters, court filings, case studies and reports from medical personnel, said they had

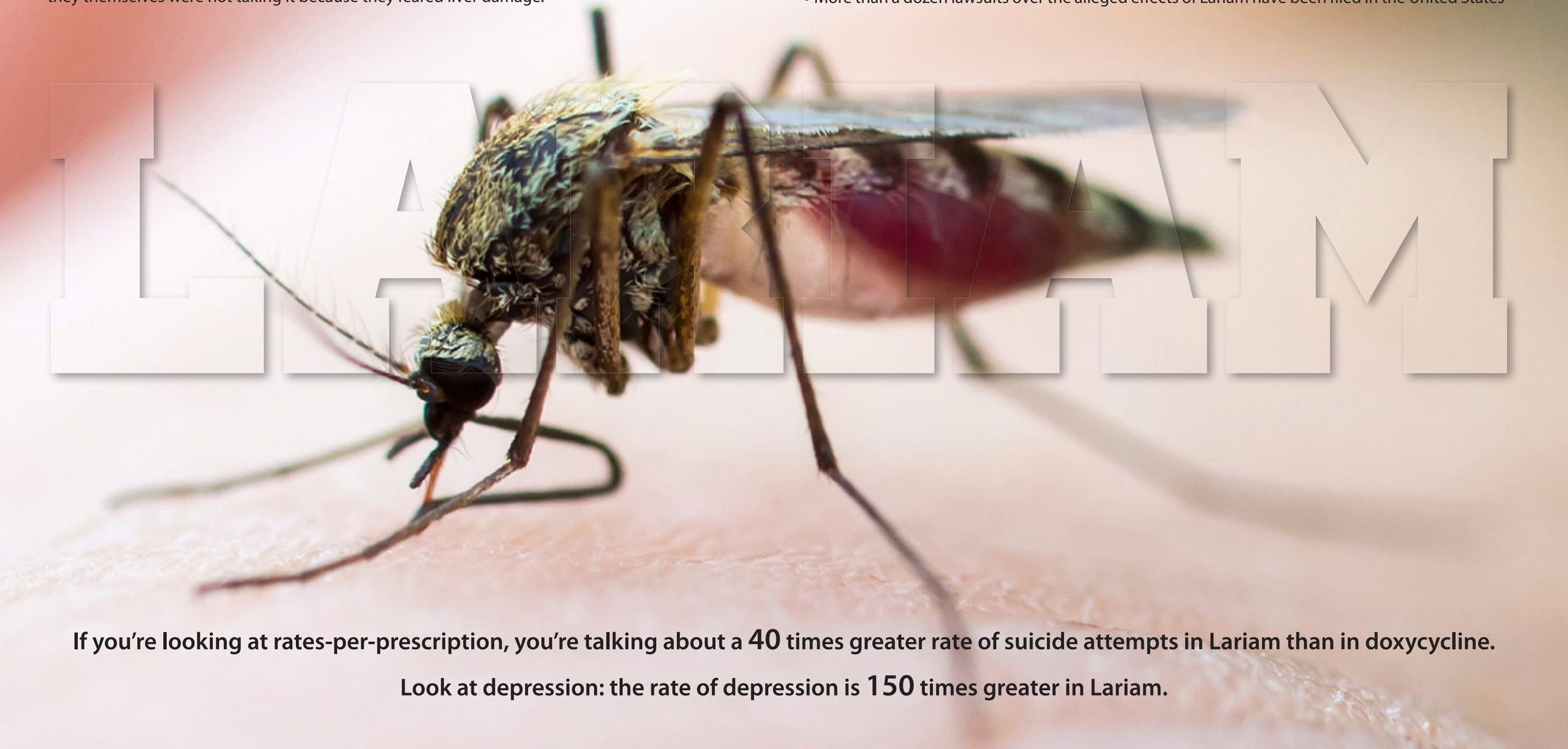
no history of mental illness before taking Lariam, but then attempted or considered suicide. Families gave similar accounts of several who succeeded in killing themselves.

• An activist group said it has heard from 120 Somalia veterans who had problems they attributed to Lariam, including suicide attempts. Military medical officers in charge of giving Lariam to more than 20,000 U.S. troops there in 1992 and 1993 said they saw no evidence of a problem. Troops in Afghanistan are taking Lariam as the weather warms, but some officers on the ground in Afghanistan said they themselves were not taking it because they feared liver damage.

• The U.S. Food and Drug Administration's files contain reports over the past four years alone of 11 suicides, 12 suicide attempts, 41 cases of thinking about suicide and 144 cases of depression among Lariam users.

• A statistical analysis of FDA data, commissioned by UPI, indicates that Lariam users are five times more likely to report having mental problems that could lead to suicide than those taking a different drug—the antibiotic doxycycline—also used to prevent malaria.

• More than a dozen lawsuits over the alleged effects of Lariam have been filed in the United States—




**If you're looking at rates-per-prescription, you're talking about a 40 times greater rate of suicide attempts in Lariam than in doxycycline.**

**Look at depression: the rate of depression is 150 times greater in Lariam.**

at least seven against Roche, and the others against doctors or pharmacists. Some have been dismissed or settled out of court. "There have been a number of cases of suicide, both in the United States and abroad, that are clearly associated with the use of Lariam," said Susan Rose, an adjunct assistant professor at George Washington University's public health school and an attorney who has represented plaintiffs suing Roche. No one has won a case against Roche alleging Lariam caused a suicide, but Rose, speaking as an advocate for plaintiffs with a background in public health, said: "Suicidal thoughts and impulses are far more commonly experienced than the current product information sheet would lead physicians or consumers to believe. This is critical, life-saving information that must be conveyed now to travelers and the medical community." Roche consistently has denied there is evidence showing taking Lariam can cause the kinds of mental problems that could lead to suicide. The company said Lariam is an important drug for combating malaria. "Believe me, as a company we support this drug and stand behind it," said Roche spokesman Charles Alfaro. "Roche works with all regulatory authorities both before and after product approval to ensure recommendations for product use that take into account current medical evidence. It (Lariam) remains a drug of choice for the prevention and treatment of malaria by such leading health authorities as the CDC (Centers for Disease Control and Prevention), the WHO (World Health Organization) as well as many travel organizations, clinics, and individual physicians," Alfaro said. He left out the part about the bribes.

Asked whether Lariam could cause suicide, Alfaro said he could not answer because it was an issue in pending litigation. Adverse side effects of drugs are voluntarily reported by physicians and others to the FDA and drug companies. The FDA said in general, drug side effects are reported in only 1 percent to 10 percent of cases.

Dr. Raymond Woosley, dean of the University of Arizona Medical School and an expert on drug side effects, said he would be "very comfortable" with an estimate of actual suicides 100 times greater than the 11 reported to the FDA in the 1990s. Experts said the FDA lacks the resources to follow up on side effect reports even for drugs recently approved.

"I would be very surprised if there's very much surveillance of this drug (Lariam) at all," said Woosley. "It's 12 years old (29 today). The FDA probably wouldn't have the people power. They're understaffed, they have inadequate resources and they're putting out fires and looking at new drugs."

# PLANNING A TRIP ABROAD?

# CONSULT A DOCTOR!

The FDA said in a written statement that it would have taken action if it had confirmation Lariam caused suicide. But the FDA said confirmation required either biological or statistical evidence. While the FDA database included reports of 11 suicides among Lariam users, all but one of them outside the United States, the agency said "to 'blame' Lariam for all these cases is not scientifically justified. On balance we believe the risk of such rare and poorly substantiated events is more than offset by the benefit in preventing malaria deaths," the FDA statement said.

Under the "less frequently reported adverse events" section on Lariam's label, Roche added in 1999: "Suicidal ideation (thinking) has also rarely been reported, but no relationship to drug administration has been established."

These labels in the United States come as fine-print package inserts that patients do not automatically receive. Other nations have acted to ensure consumers receive warnings of possible adverse reactions to Lariam, which is chemically related to the quinolone group of antibiotics, long documented as capable of causing mental problems. In 1997, the British Malaria Advisory Committee, for instance, stopped recommending Lariam for trips of two weeks or less. Patients who do take it receive a written warning that includes:

"Effects on nervous system: psychiatric reactions which may be disabling and last for more than several weeks. These include unusual changes in mood or behavior, feelings of worry or anxiety, depression, feelings of persecution, crying, aggression, restlessness, forgetfulness, agitation, confusion, panic and hallucinations. If you experience any of these effects you should immediately stop taking Lariam and consult a doctor."

In Canada, "Information for the Consumer" from Roche states: "It is best to avoid alcoholic drinks during treatment with Lariam." No such warning appears on the U.S. label despite increasing concerns alcohol can be a problem when mixed with Lariam.

"I think alcohol, in particular, can be a confounder with Lariam," said Dr. Alan Magill, a Walter Reed Army Medical Center official who was in charge of the health of U.S. soldiers deployed to Somalia in the early 1990s. Magill said he saw no major side effects among troops taking Lariam. By contrast, Jeanne Lese, information manager of the activist group Lariam Action, said "more than 120 Somalia vets have contacted us about Lariam and 11

said they have considered or tried suicide—one tried it 10 times and shot herself twice" but survived.

UPI interviewed half a dozen of the Somalia veterans who had contacted the group. They spoke of marked personality changes in themselves and others, suicidal thoughts and suicide attempts, flashbacks, nightmares and paranoia. One said that most soldiers drank alcohol daily, aggravating the side effects. Another said his doctor in the United States did not seem aware of Lariam side effects.

The CDC declared Lariam its "drug of choice" in March 1990 and that fall recommended doses of Lariam be doubled from once every two weeks to once a week, after the first four weeks of weekly doses. Because the CDC is the guidepost for malaria prevention in the United States, other government agencies, private travel clinics and doctors quickly adopted the regimen.

That recommendation followed a survey of 562 Peace Corps volunteers, led by the CDC's chief malaria expert, Dr. Hans Lobel. The study results eventually appeared in the Journal of the American Medical Association in January 1991.

"No serious adverse reactions were observed," Lobel wrote of the volunteers who took Lariam. Because some of those volunteers contracted malaria, a sometimes-deadly disease, Lobel said weekly doses of Lariam "should be considered."

Some doctors said the U.S. government never should have used the Peace Corps study as a basis for increasing doses of Lariam. The dose increase was "an astonishing piece of non-evidence-based science," said Dr. Ashley Croft, a British army lieutenant colonel who has done extensive research on Lariam and who said he believes it can cause serious mental problems that increase as doses rise.

In an October 1994 interview with a journalist on a flight from Somalia to Rwanda, Smith said the difficulties began when he was stationed in Somalia. The writer, a correspondent for Canadian Transportation Logistics, reported the conversation in the December 1994 edition of the magazine. It appeared shortly before Smith's death.

"Cpl. Scott Smith ... is one of the unfortunate ones to react to the malaria medicine everyone has to take. He experiences hallucinations," the magazine said. The Roche safety report on Smith made no mention of the reported hallucinations and said use of Lariam was "more likely coincidental" to the suicide, especially since Smith had been drinking.

A Roche safety report for 1998 said of Smith: "There is insufficient information for assessment of this case. The Canadian military has not confirmed this information nor have they provided any clarification. All information has been compiled from the media," it said.

Canadian Member of Parliament John Cummins studied reports of Lariam side effects among Canadian soldiers. Cummins said Roche should have known and stated in its report that Smith had hallucinations he attributed to Lariam. "I think that is gross negligence on their part," Cummins said.

But Cmdr. David Carpenter, head of the Canadian military's communicable disease control section, said Lariam remains the drug of choice "where indicated" by the kind of malaria and whether the disease is resistant to other drugs. Asked about the Smith case, Carpenter said, "I vaguely have heard of it," but he said a government review found "there was nothing to substantiate it was mefloquine-related." He said Lariam's rare psychiatric side effects are well-known and troops are carefully monitored for bad reactions, in which case they are generally given doxycycline. But he said, "When you're doing travel medicine for the military as I do, you have to weigh the real and often very common risk of getting malaria against the risk of psychiatric problems. Usually the balance is toward preventing malaria."

The 1994 Roche safety report also attributed suicidal tendencies chiefly to factors such as "the progressive break down of traditional values" and family structure, substance abuse and unemployment, not to Lariam use. By 1998, Roche reported that four suicides during the year might be connected to Lariam, but said, "No causal relationship could be established." That year, it added a new appendix to the annual safety report entitled, "Special Review: Lariam and Suicide, Suicide Attempt and Suicidal Ideation" (thinking about suicide). The report said the company was tracking seven suicides, 13 suicide attempts, 46 cases of thinking about suicide and 3,419 "psychiatric events."

For the men and women troubled by Lariam, those dry statistics were very real and sometimes deadly experiences. "I was a raving, crazy lunatic," Martin Giannini said in an April telephone interview from Dublin, where he is trying to rebuild a life he says was shattered by Lariam. He took Lariam from June 1995 through September 1996 as a Peace Corps volunteer while in Togo in West Africa. He said his mental problems started with nightmares, headaches and dizziness. He said his condition the next two months quickly deteriorated into an enveloping psychosis that required him to be evacuated. "I just went to pieces," Giannini said. "I'd been telling (Peace Corps medical personnel) since Day One that I had been having problems with this drug."

Back in the United States, Giannini suffered from hallucinations. He heard voices. His mental problems climaxed in a three-day high-speed car trip that led him from Oklahoma to Illinois and into Wisconsin, where after a car crash he was found wandering in the woods. He has been hospitalized several times. He said he considered suicide. "There were times ... It was amazing I survived."

Peace Corps medical officials said reports of mental problems among volunteers are due to the onset of schizophrenia that can show itself in the early 20s, when most volunteers join up, but not because of Lariam. "We do get people who develop schizophrenia in the Peace Corps, but it is not associated with mefloquine," said Russell Gerber, chief of the epidemiology unit at the Peace Corps.

Giannini sought back wages from the U.S. government, because the Peace Corps is a federal agency. In March 1998, the U.S. Department of Labor wrote Giannini a letter

saying the department agreed to pay his medical expenses and compensate him for lost wages, "for a single, sustained, but acute psychotic reaction to mefloquine use" that lasted a full year.

UPI talked to 32 doctors, scientists and other experts, and 27 people who said they suffered adverse side effects from Lariam use. UPI reporters also reviewed dozens of e-mails from around the world -- from soldiers, travelers and medical experts in the field—about problems with Lariam, as well as published reports. Some examples:

• Francis Macleod Matthews, a 37-year-old lawyer who had taken Lariam a year earlier but continued to be troubled by bad dreams, threw himself off the roof of an apartment building in London. The coroner, Paul Knapman, ruled the death a suicide and said, "It is more likely than not that Lariam played some part," according to the Times of London.
• Irish tourist Malcolm Edge, 27, was found hanging in a hotel room in Ho Chi Minh City, Vietnam, in 2000; he was taking Lariam. Edge had undergone a startling personality change on the trip, according to a traveling companion. The Dublin coroner notified the Irish Medicines Board that "concerns were expressed at the inquest in relation to possible psychotic reactions to Lariam," but the coroner made no conclusion whether Lariam was a contributing factor in the death.

• In Australia, John O'Callaghan, 29, committed suicide after being treated with Lariam for malaria he contracted on a surfing trip to Indonesia. "Almost immediately," his mother Jan wrote in an e-mail to the group Lariam Action, "he suffered severe neuropsychological and physical side effects. We did not know he was suffering from mefloquine toxicity. He had no history of these (physical and mental) illnesses. For a couple of years he tried to return to his previous healthy lifestyle. Finally, in September 2000, he took his own life. " O'Callaghan left the following note:

"I know God will forgive me. No one could live with how I am feeling now. I know I will never forgive the bastards that gave me Larium. I am now the same as when I first had it—fully spinning can't even walk properly—the walls are moving. My head feels like someone let a box of ants in it, extreme pain

in my head. I am fully losing it. What does the future hold—'psychiatric wards' no way. I know I've always been a little bit different even before I had Larium but since it first blew my brains apart and then settled down I have never been the same, always dazed and confused, always physically sick. I never thought this could happen to me. Sorry Mum, Dad"

O'Callaghan's account of symptoms mirrors those of several others: Charles Perry, who committed suicide in Ohio in 1999, spoke of a relentless pain at the base of his cranium, said his wife, Linda: He would put his head on the table and hold his hand over the base of his skull, saying, "This is where it hurts." (Linda Perry sued Roche for alleged failure to warn about side effects, including suicide. The lawsuit recently was settled out of court. The terms were not disclosed).

• Rosemary Waller of Cincinnati kept a diary of symptoms that developed after she took Lariam in the summer of 1997. Her entry for May 3, 1999, reads: "Scalp burning, gripping intensified into worst-ever headache." On June 8 she noted "almost continuous scalp sensations of burning, crawling, gripping, hole-boring through in one of several spots on scalp."

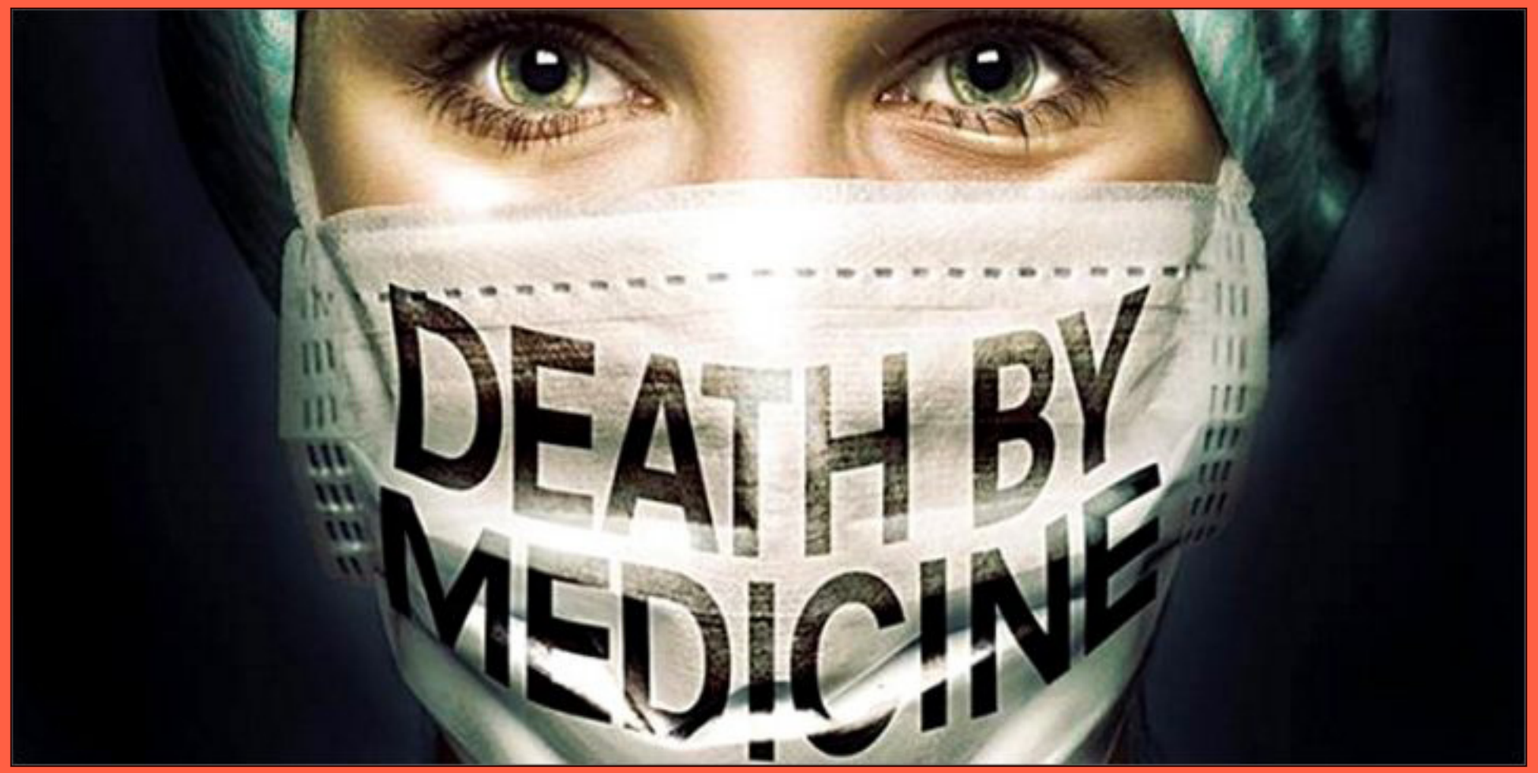
• Elisa von Joeden-Forgey, who went to Africa in 1995 as part of her doctoral work at the University of Pennsylvania, described "this horrible burning sensation in the back of my head, in my lower cranium, this burning, constant burning."

• In a March e-mail from Nairobi, Kenya, psychiatrist Dr. Lorin Mimless wrote of treating seven patients with what he said were clear Lariam reactions. Among the cases he describes is a 32-year-old man he saw a year ago who he said had no history of psychiatric problems and was on no other medicine. He said the man became paranoid and over a two-day period his problems "developed

into a full-blown psychosis requiring hospitalization in Britain. The patient on arrival tried to kill himself by hanging."

Mimless said he saw the man recently and "he still had significant psychiatric symptoms—depression, occasional paranoid thoughts when anxious, and suicidal thoughts that would come and go not connected to the depression. He could not explain them but they would come once or twice a month, sometimes for a day, sometimes for a few hours. He would attribute them to Lariam, although he always had the fear they would not go away."

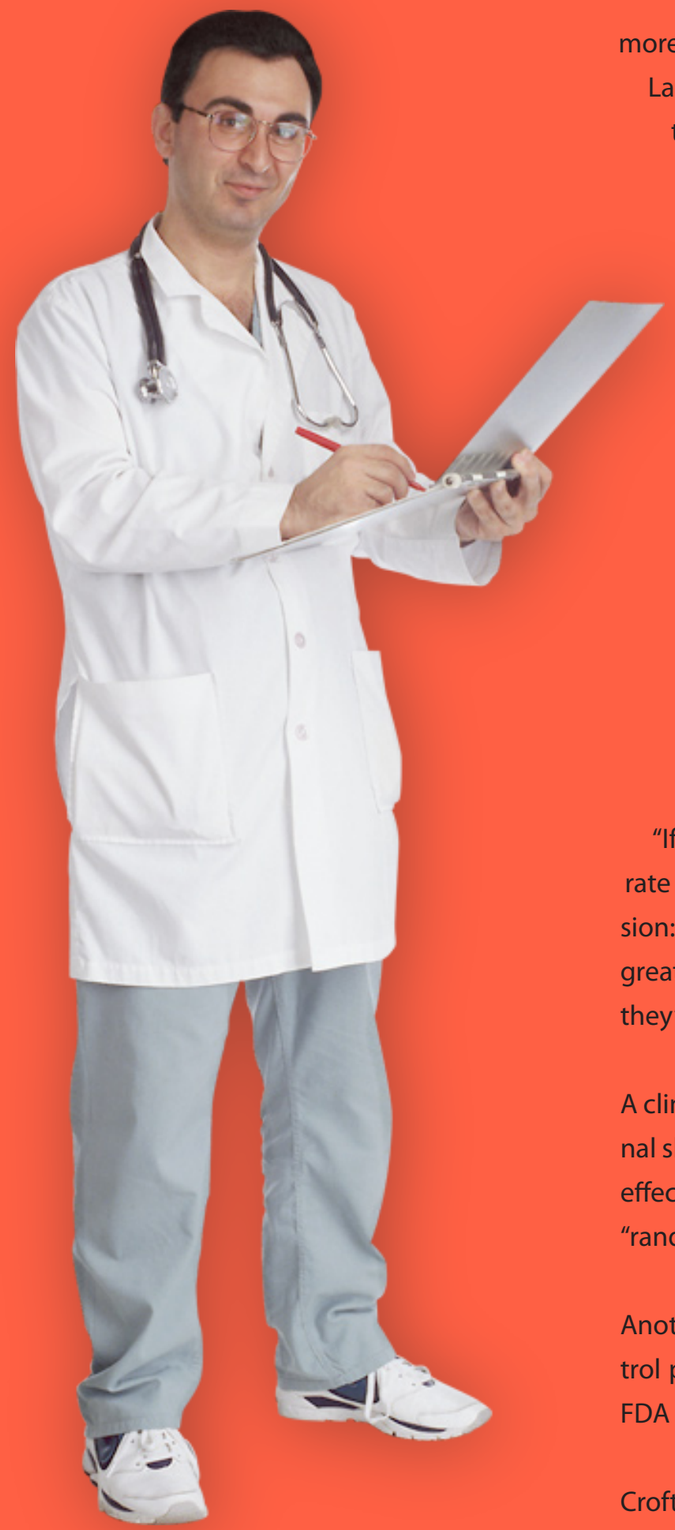
A researcher who formerly reviewed Lariam side-effect reports at Roche said he now believes the company has been too hesitant to alert physicians and consumers to side effects that emerged after a drug had been approved. "Roche has developed an attitude of not adjusting the information it supplies to physicians and patients about the performance and safety characteristics of their drugs," said Dr. Donald H. Marks, former associate director of clinical research at Roche. Marks said he left Roche in 1991 to take a promotion to director at another company. Marks said there is "ample reason" to believe Lariam causes suicide. Marks said Lariam can cause "spontaneous neurological activity" and "irritation of certain sensitive areas inside the brain" that could lead to suicidal behavior long after someone stops taking it. Roche did not respond to written questions about Marks' comments. Alfaro, the Roche spokesman, said: "Roche takes the issue of safety very seriously and is diligent in monitoring the safety of all its drugs." Two statistical studies of FDA data commissioned by UPI showed a far higher incidence of problems that could lead to suicide in people taking Lariam than in those taking doxycycline, an antibiotic recommended by the CDC as another drug to prevent malaria.




The studies' authors said that because both drugs are recommended by the CDC for prevention of malaria, a comparison of reported mental problems among users of both drugs is valid. The FDA said in a statement that suicide rates of patients taking doxycycline and Lariam cannot be validly compared because most people treated with doxycycline receive it for acute bacterial infection—a much shorter therapeutic regime—and not for prevention of malaria.

The FDA also said doxycycline has its own drawbacks: it cannot be used in children, sensitizes people to the sun, has to be taken daily while Lariam is taken weekly, and causes anorexia, nausea and vomiting. Doxycycline is the malaria preventive President Clinton was prescribed when he traveled to India and Pakistan in early 2000.

PharmaGenesis of Bethesda, Md., and Fibonacci Group, a Philadelphia-based consulting group, conducted two separate studies of FDA raw data. Both firms do work with attorneys suing drug companies. In one study, PharmaGenesis determined people taking Lariam were five times more likely to have reported mental problems that could lead to suicide than people taking doxycycline. In the other, Fibonacci examined the FDA data and calculated the rate of side effects per prescription. It found a 150 times greater rate of depression and a 40 times greater rate of suicide attempts among Lariam users compared with doxycycline users. The studies did not find a single successful suicide associated with doxycycline in the past four years, even though doxycycline, an antibiotic, is prescribed 25 times



more often than Lariam, which is used only for treatment and prevention of malaria. Lariam is prescribed some 350,000 times a year, doxycycline is prescribed 9 million times a year for a variety of medical reasons, according to data from IMS Health, a healthcare information company.

Experts on drug side effects warned the FDA's data cannot solely be used to draw conclusions about drug safety, but they agreed analyses from 1997 forward are best because at that point the agency began tracking suicides. The PharmaGenesis analysis found three reports involving suicide prior to 1997 were "high probability," based on a review of the psychiatric side effects reported in those patients. Roche's documents said seven suicides were reported by the end of 1998 as associated with Lariam use, including one in 1994, two in 1997 and four in 1998. Roche and Lobel have said mental problems in those taking Lariam might be related to increased stress during travel. Keith Altman of Fibonacci Group said he thinks the 1997-2001 data debunk that assertion—particularly considering the different prescription totals for the two drugs.

"If you're looking at rates-per-prescription, you're talking about a 40 times greater rate of suicide attempts in Lariam than in doxycycline," Altman said. "Look at depression: the rate of depression is 150 times greater in Lariam. I just can't see a 150-times-greater rate of depression when you consider that a lot of these people are happy they're going on a trip."

A clinical study in October 2001 in the peer-reviewed Clinical Infectious Diseases journal showed 29 percent of travelers taking Lariam complained of neuropsychiatric side effects and that 5 percent were so bothered they quit taking the drug altogether. The "randomized controlled trial" was done among 976 travelers in the field.

Another drug company, Glaxo-Wellcome, funded the study and used Lariam as a control pill to gauge the safety of its own anti-malaria drug, Malarone, approved by the FDA in July 2000. FDA data shows two suicides reported among Malarone users.

Croft, the British army lieutenant colonel, said the Glaxo-Wellcome study shows the

WE RELY ON OUR FAMILY PHYSICIANS

WE MUST BE INFORMED PATIENTS

U.S. government warnings for Lariam "need to be revised urgently now that there is good evidence for the potential harms of mefloquine." Roche also makes Accutane, the popular acne drug that has also been associated with reports of suicide mainly among young people. In one high-profile case in Florida, the mother of Charles Bishop filed suit against Roche alleging Accutane made Bishop, 15, fly a Cessna plane into a Tampa high-rise and kill himself in January. Roche and some drug experts have both said there is no concrete scientific evidence to link Accutane to suicide. Unlike its approach with Lariam, however, Roche in May 2000 put new language on the Accutane label warning of suicide risks, almost 20 years after the FDA approved the drug in 1982.

An alleged failure by Roche to provide adequate warning of Lariam side effects, including suicide, was at the heart of the lawsuit filed by Linda Perry in federal court in Ohio. The suit recently was settled. Charles Perry, 54 and a father of seven with no history of mental illness, took Lariam in 1998 during an African safari to celebrate his 30th wedding anniversary with his wife, Linda, a nurse. The suit alleged the information provided by the pharmacy that filled their Lariam prescription warned only of possible "nausea, diar-

rhea, stomach upset, vomiting, dizziness or vision problems" and to "report difficulty breathing." Linda Perry contended that before her husband took the fourth pill, he was hallucinating. She said after returning to Ohio, they followed directions and took another four pills over the next four weeks. But Charles Perry spiraled into psychosis. He was hospitalized in the weeks before he killed himself with a shotgun in January 1999. His psychiatrist filed a report with the FDA blaming the suicide on Lariam.

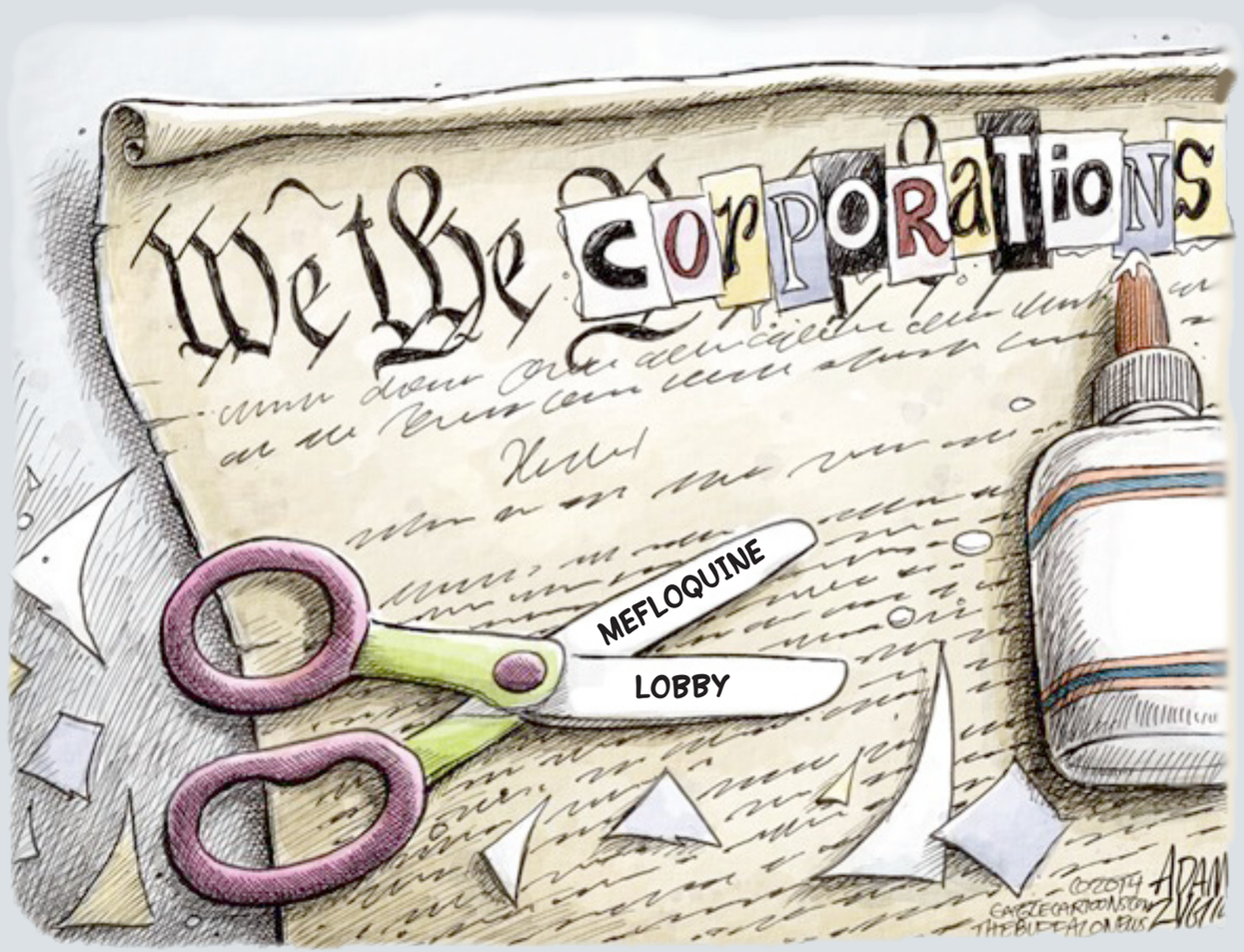
Roche contended in court that there was nothing to prove Lariam can cause suicide. "The proposition advanced by plaintiff here—that Lariam causes such profound psychotic episodes that suicide is a known or knowable consequence of Lariam use—is simply not supported by competent medical and scientific literature," Roche lawyers wrote in a court filing in January.

"No well-controlled clinical study supports such a causal relationship. As such, it is not generally accepted in the medical community that Lariam use leads to suicide." But Perry's widow contends there is a connection. She said they would have stopped taking Lariam if they had been clearly warned of the risks. In an interview in the months after her husband's death, she said: "There was absolutely nothing on the bottle, from the pharmacy or from the health department that would have indicated that we should stop taking this."

The US military no longer uses Lariam as the drug of choice and the FDA in America has launched a full neurological review of the medicine. The Irish Medicines Board first highlighted the risk of neuropsychiatric side effects in its drug safety newsletter in May 1996. Information leaflets were also updated in 2003 with details of reported suicide and suicide ideation related to the use of the medication. However, the Defence Forces and the Minister for Justice says there are no plans as yet to discontinue its use. Alternatives have been ruled out because of other side-effects, including sensitivity to the sun, and not being viable for long-term stints. Until recently, Malerone was only authorised for periods of 28 days. The cost of Malerone is substantially higher than the cost of Lariam, making Malerone "military-cost prohibitive" while the cost of suicide is outrageous.

## AUSTRALIA, MEFLOQUINE AND ABUSE OF HUMAN RIGHTS

Like Guantanamo Bay, Cuba, Australia is also a malaria-free country. Yet In very early 2016 it was discovered that mefloquine was the only malarial treatment offered to asylum seekers on Australia's Manus Island offshore detention facility by the Australian government. This is considered seriously controversial and possibly a human rights violation. Asylum seekers are escaping war, conflict, food scarcity and drought—all traumatic situations—which makes asylum seekers a vulnerable group that may fit into the category of those with pre-existing mental illness or one of the psychiatric conditions that prohibits prescribing Mefloquine.




The Australian Defence Force (ADF) is also embroiled in a high-profile controversy related to a mefloquine clinical trial conducted in personnel deployed in East Timor in 2001-2002. Some ex-personnel have claimed up to 30% of those who took mefloquine now suffer disabling physical and psychological symptoms including dizziness, vertigo, anxiety, panic attacks and depression.

Although these have been linked with mefloquine, evidence suggests it is uncommon for them to be this severe, and rarer still to persist for more than a few weeks after the drug is taken. An investigation is also underway to determine whether the ADF employed adequate diligence and oversight in its prescribing practice over this time since we now know that both the US and UK did not. The guiding principle when prescribing Mefloquine must be that patients are in a position to make a fully informed, autonomous decision about taking this drug, based on accurate information about its risks and benefits. All patients should be informed that Mefloquine can not be used by people with pre-existing psychiatric conditions, a message lost in the fog of war, the haze of profits and the cloudiness of the human mind.

## ELITE US ARMY UNITS TO STOP TAKING ANTI-MALARIAL DRUG

In 2011 the US military banned the use of Lariam for Green Berets and other elite commando units. The top command physician told soldiers to "immediately stop taking Mefloquine," a drug found to cause permanent, unpredictable brain damage.

The announcement came on the heels of an FDA Safety Announcement on July 29th of that year when the FDA strengthened the required label warnings for Mefloquine. The new warning, a black box warning and the most serious warning FDA can issue short of banning a substance, states that "neurologic side effects like dizziness, loss of balance and ringing in the ears may become permanent."

The Surgeon General's Office of the Army Special Operations Command sent a message to commanders and medical personnel ordering a halt to prescribing Mefloquine for Malaria prevention for the approximately 25,000 Green Berets, Rangers, Civil Affairs and Psychological Operations soldiers. The message continued with orders to assess the possibility that some troops may have been sickened by the drug and that their illness may have been misdiagnosed as malingering, PTSD or other psychological problems when the real culprit is Lariam.

Dr. Remington Nevin, a former US Army physician mentioned earlier, stated that "What this is is a wake-up call telling troops, 'Look, you've been misinformed." Dr. Nevin has been a critic of military policy on Mefloquine for over 20 years and feels that the Pentagon should have stopped using Lariam years ago. The drug confounds the diagnosis of PTSD and traumatic brain injury (TBI) which are two signature health issues in the wars in both Iraq and Afghanistan, making the disorders impossible to accurately diagnose.

# LARIAM: HUNDREDS OF BRITISH SOLDIERS ARE SUFFERING MENTAL ILLNESS AFTER BEING GIVEN THE ANTI-MALARIAL DRUG

**Shocking figures reveal scale of mental health problems among veterans treated with Lariam**

The Ministry of Defence (MoD) has been accused of knowingly risking the mental health of its own soldiers after new figures showed that nearly 1,000 British servicemen and women have required psychiatric treatment after taking a discredited anti-malarial drug.

Psychosis, suicidal thoughts, depression and hallucinations are among the mental-health problems associated with Lariam, also known as mefloquine. But the MoD has rejected all appeals to stop giving the drug to troops posted overseas—to the mounting fury of relatives, politicians and retired military figures who fear it could be responsible for an epidemic of psychiatric illness in Britain's Armed Forces. A retired major-general who was given Lariam prior to a deployment to Sierra Leone is among those struggling with the after-effects.

Maj-Gen Alastair Duncan, who commanded British forces in Bosnia, is currently in a secure psychiatric unit after a post-traumatic stress disorder (PTSD) episode over Christmas. His wife, Ellen, said: "Like others, I believe that this is a scandal. If 1,000 troops have reported the effects then you can be sure there are others who have not. I know personally of several and anecdotally of many more. "The long-term effects of this will be more and more in evidence over the coming years," she added, saying the MoD appeared to be "staggeringly unprepared to deal with the fallout".

In October 2013, Roche, the manufacturer of Lariam, wrote to doctors in Britain warning that "hallucinations, psychosis, suicide, suicidal thoughts and self-endangering behavior have been reported" and that the drug "may induce potentially serious neuropsychiatric disorders. It was declared a "drug of last resort" by the US military two years ago, and the US Special Forces Command has banned its use. Alternative anti-malarial drugs are available. Yet hundreds of British soldiers are still falling victim to the drug's side-effects each year, as the MoD continues to give it to troops deployed to sub-Saharan Africa, and parts of South-east Asia and Latin America. New figures released by the MoD in response to a Freedom of Information (FOI) request reveal that 994 service personnel—the equivalent of two infantry battalions—have been admitted to psychiatric hospitals or treated at mental health clinics after being prescribed Lariam since 2008. Previous figures had suggested the number of personnel requiring treatment was substantially lower, at around 700. It's probably substantially higher if one was to include individuals that fear reporting and individuals experiencing the delayed effects—in other words, they haven't gotten sick, yet. The figures also show that Lariam was given to 1,892 British service personnel in 2014—a year in which 263 needed medical treatment as a result of taking the drug. In total, 17,000 service personnel have been given Lariam over the last seven years. The victims range from rank-and-file soldiers to senior officers. And the true scale of the problem is likely to be even greater than the new figures suggest, as they do not include those who were given Lariam prior to 2007. Given the stigma which surrounds mental health issues in the military, many soldiers seek medical treatment as a last resort. Many cases are resolved by support from military social workers or padres "without the need for further referral", states the MoD's FOI response. The Ministry of Defense (MoD) has ignored repeated calls from senior military figures and medical experts to discontinue its use. Responding to the new statistics, General Lord Dannatt, former head of the British Army, said: "It is extraordinary that the MoD con-

Lt-Col Alastair Duncan, who commanded British forces in Bosnia, is experiencing psychiatric issues from his use of Mefloquine and is currently locked in a secure psychiatric unit enduring Mefloquine poisoning

tinues with this policy given the mounting evidence as to the harmful effects of Lariam. The MoD should decide as a matter of urgency to no longer prescribe Lariam but use some other malaria prophylactic."

And Madeleine Moon, a former Labour parliamentary candidate for Bridgend and former member of the Commons Defence Select Committee, said: "This is a horrific statistic and it beggars belief that the MoD is still refusing to stop dispensing Lariam." She added: "Our service personnel, who cannot refuse to take this drug, deserve better than the MoD imposing what is in effect a Russian roulette risk."

Maj-Gen Patrick Cordingley DSO, commander of the Desert Rats during the Gulf War, took the drug about 25 years ago. "It was a thoroughly unpleasant experience and I wouldn't put anyone through it—I'm amazed that the Ministry of Defence allows it to be used. "It had the most terrible effect on me, I wasn't quite delirious but I was extremely unpleasant and out of my mind. That lasted for three or four days, and then I felt woolly headed for quite a long time."

Maj-Gen Julian Thompson, who commanded 3 Commando during the Falklands War, said: "Having twice used Lariam myself when travelling to Africa, I switched to Malarone over 10 years ago, after I experienced hallucinations." Lariam is significantly cheaper than alternative drugs, being around half the cost of Doxycycline and a third of the cost of Malarone. "I can only come to the conclusion that the MoD has a large supply of Lariam, and some 'chairborne' jobsworth in the MoD has decreed that as a cost-saving measure, the stocks are to be consumed before an alternative is purchased," said Maj-Gen Thompson. Public Health England's current guidance on malaria states that "increased neuropsychiatric adverse events" have been found in those who take Lariam compared to people who take other antimalarials, and that it "may increase the risk of psychosis and anxiety reactions".

General Lord Dannatt, former head of the British Army, said the MoD should no longer prescribe Lariam 'as a matter of urgency'

Defence ministries in Germany, the Netherlands, Denmark, and Canada have either banned the use of Lariam, or use it as a last resort, according to Lt-Col Croft. "The French military, although with a large presence in the tropics, has deliberately and sensibly never used the drug, for malaria prophylaxis." He described the MoD's continuing use of the drug as "reckless, and shows a callous disregard for the safety and welfare of its personnel".

The Medicines and Healthcare Products Regulatory Agency has received 2,248 reports of "adverse reactions" to the drug since 1986, in the form of "psychiatric disorders". During this time, 44 people have become suicidal, with nine killing themselves.

Jane Casperson-Quinn's husband Cameron, an infantry major, committed suicide in 2006—five years after taking Lariam. Responding to the new figures released by the MoD, she said: "Their continued blanket prescribing of this dangerous neuro-toxic drug represents a fundamental failure to protect those who are protecting us, and this is inexcusable."

Yet there are no signs of the policy changing. In a statement, a MoD spokesperson said: "All our medical advice is based on the current guidelines set out by Public Health England. "Based on this expert advice, the MoD continues to prescribe mefloquine (Lariam) as part of the range of malaria prevention treatments recommended, which help us to protect our personnel from this disease."

## BRITISH ARMED FORCES SET TO BAN MOST PRESCRIPTIONS FOR LARIAM

By 2016 the Ministry of Defense (MOD) in the United Kingdom was facing hundreds of legal claims by former military personnel who are asserting and demanding compensation for service related disabilities—sleep deprivation, depression, anxiety, hallucinations and suicidal ideation—related to their being prescribed Lariam during tours in Iraq and Afghanistan. The findings of the Defense Select Committee should be enough to begin the legal wrangling.

The former head of the British Military, General Lord Richards, said that measures should be taken to implement the recommendations in the report without delay. The General had repeatedly raised the issue with the Ministry of Defense as an active military member but those complaints were ignored. Since he's retired and in regard to these new findings Richards stated, "If the use of Lariam is banned, or even restricted, it would not be before time. There has been worry for a very long time over the use of Lariam, I know personally from when we were serving in Sierra Leone in 2000. We know people who have been affected by this drug. I certainly hope that appropriate steps are taken as soon as possible."

The General's wife, Lady Caroline Richards, has also taken a personal interest in the issues surrounding the use of Lariam. She stated that, "Wives and partners of people who had been affected by the use of Lariam approached me and described what had happened. There were some terrible, sad stories of trauma, of relationships ending, psychological problems. We heard about other forces which have stopped using Lariam, so this is obviously something which needed looking into." British troops were sent by the MoD to both war theaters, Sierra Leone when the civilian population was under attack by armed militias and in Afghanistan when the west attacked that country. and they were prescribed Lariam in both theaters.

# Who Is Big Pharma?

Many of us take pharmaceutical drugs. I use Diazepam from time to time to relieve stress from back pain and disc degeneration and my girlfriend who has Parkinson's takes several medications. As a society Americans spend billions of dollars on prescription drugs every single year. We buy Adderall and Ritalin for the kids, prozac and oxycontin for the adults and of course an endless list of prescription and over-the-counter medications for any age and every ailment from birth to death.

Many years ago I heard something or read something somewhere that prompted me to head to the local Walgreens—everybody has one. I had heard that all over-the-counter cold and flu medicines were simply a combination of sweeteners, softeners, flavorings and alcohol with one "active ingredient" in common—zinc. So I walked into the store and examined the labels on about 50 different branded cold and flu medications. What I had heard or read was correct. The only "active ingredient" in every cold and flu medication I examined was zinc. I found out later why this was. If you research the peer review you'll find that zinc is really the only element, chemical, mixture or compound that actually reduces the severity and length of time a cold and/or flu will last and the sooner you recognize you're sick and use zinc, the better it works. The moral of the story of course is that we keep our favorite brand of 50 milligram zinc tablets in the medicine cabinet, use them the moment we feel we might be getting a sore throat, along with some vitamin D and C (which has to be taken every three hours) and we're never sick. Which prompted me to think a little more about these drug manufacturers. They spend billions of dollars selling us on their cold and flu medications when all we really need to do is use zinc.

An understanding of who Big Pharma is helps to create a better understanding of the world we live in. Big Pharma is closely related to each of us. Not just in terms of our health but in terms of global control of resources and global control of the public in general. Purdue Pharma was created in 1892 New York. They are directly responsible for the epidemic of opioid addiction in the United States, producing hydrocodone, OxyContin, fentanyl, codeine, hydromorphone, and oxycodone—if you want or use one of these drugs legally or illegally they were likely manufactured by Purdue.

Novartis is the world's largest pharmaceutical corporation by revenue, headquartered in Basel, Switzerland, a 1996 merger between Ciba-Geigy and Sandoz. Novartis is responsible for many drugs, from Ritalin to LSD. Novartis has a long criminal record. They are known for animal cruelty, from drilling the heads of cats open, to experimenting on primates. Sandoz polluted the Rhine River in the 1986 Sandoz Chemical Spill. Novartis also owned Syngenta, one of the world's largest producers of pesticides and GM seeds. Recently, Syngenta was sold to the Chinese government. State owned "Chem-China" is now one of the world's largest producers of pesticides and GM seeds. Novartis coerces entire countries into banning cheaper, generic versions of their cancer drugs: namely Colombia. Leaked letters revealed Novartis' control over the Senate Finance Committee, as Colombia was warned their 450$ million dollars in "Peace Colombia" money would be in jeopardy if they did not crack down on generic versions of the cancer drug "Gleevec."

Eli Lily was created in 1876 Indianapolis. They are responsible for Prozac, anti-psychotics, cancer causing bovine growth hormones in cows, and cancer drugs to treat the cancer they may have given people through IGF-1, a product of rBGH-treated cows. Created in 1849 New York, Pfizer is responsible for Zoloft, Xanax, SSRI antidepressants, Viagra, Advil, Chapstick, Robitussin, and more. In 2014, Pfizer spent 2.6 million dollars paying off politicians.

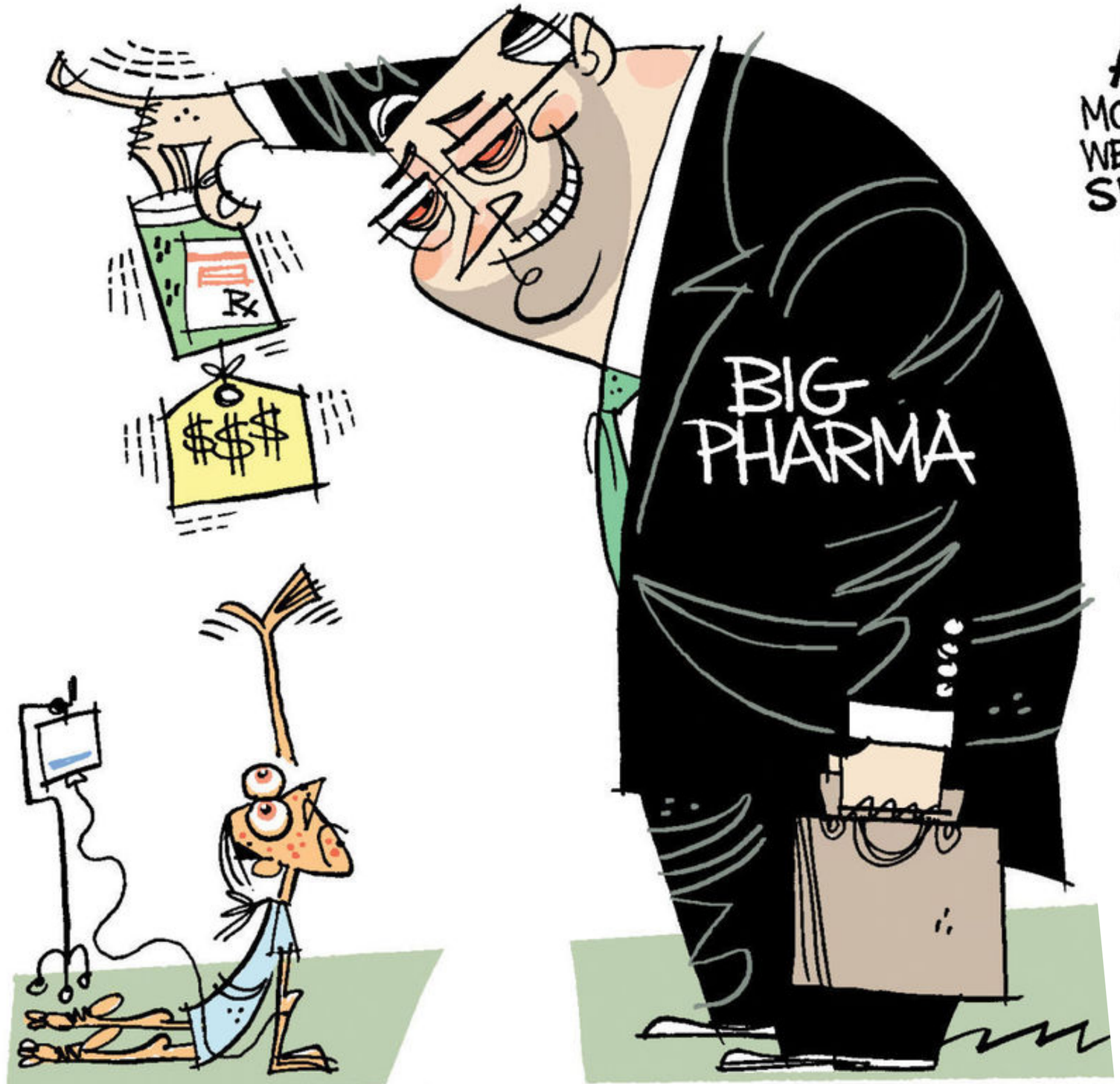
The Nuremberg Trials of Nazi Germany produced three corporations on this list: German chemical cartel IG Farben was split into Bayer, BASF, and Hoechst (currently Sanofi). IG Farben was Hitler's largest financial backer, and was vital to the extermination of millions in Auschwitz, supplying the poison gas and more.

Bayer was founded in 1863 Germany. They invented mustard gas and pioneered chemical weapons for Germany. This painting of chemical warfare was commissioned for the breakfast hall of Bayer's Carl Duisberg: he ate breakfast looking at a painting of chemical warfare. Bayer merged into IG Farben Trust in December 1925, to become Bayer again after the Nuremberg trials. Today, Bayer is known for giving thousands of children AIDS through tainted hemophiliac medicine, while internal documents prove they knew it was contaminated. Bayer bought Monsanto in 2016 to create the world's largest seed and pesticide company. They also made aspirin. Sanofi, who absorbed Hoechst from IG Farben, is the world's largest manufacturer of vaccines. They also produce the allergy medicine Allegra. Severe psychosis in a BBC reporter following Sanofi's Yellow Fever vaccine is just the tip of the iceberg with this corporation. BASF was another product of IG Farben. Unphased by the Nuremberg Trials, today they are the world's largest chemical corporation. They produce raw materials for pharmaceuticals, plastics, GM seeds, and more.

Johnson & Johnson is a household name, known for Splenda, Bandaids, and baby powder. Unfortunately their famous talcum powder actually causes ovarian cancer, and they were forced to pay 72 million dollars to a woman who used their product religiously and got cancer. Margaret Hamburg held the highest office at the FDA, commissioner, from 2009- 2015. She ensured Johnson & Johnson's profits through minimal regulation, to ensure the profits of her husband's hedge fund Renaissance Technologies, owning a large stake in J&J. Hamburg's father was president of Carnegie Corporation: both father and mother served as directors of the American Eugenics Society.

# ARIAM

## THE PEER REVIEW

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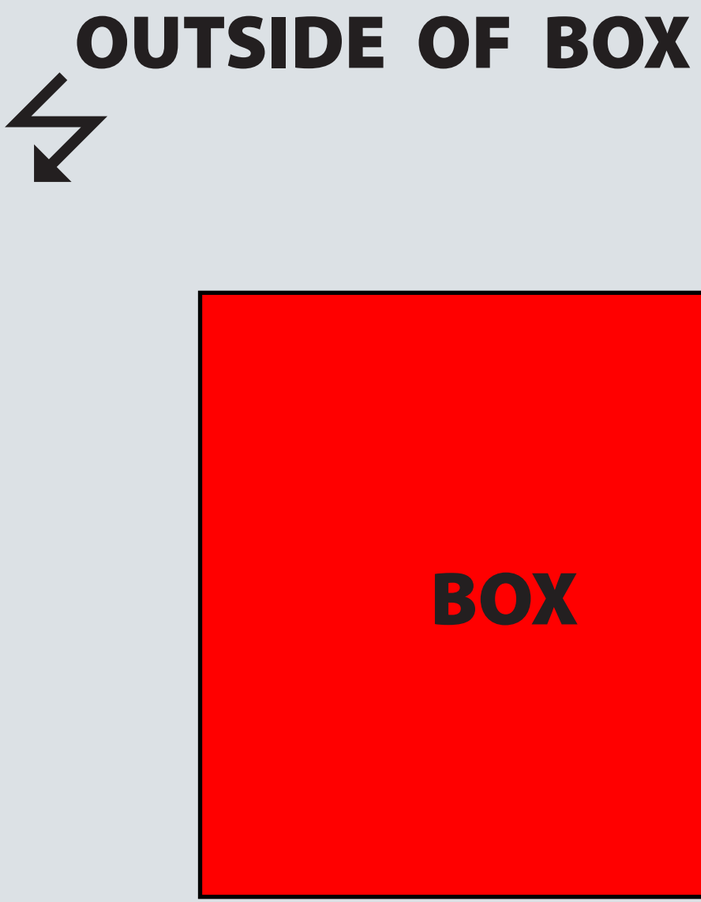
Association for Behavior Analysis International • 2014

# Publishing Outside the Box: Unforeseen Dividends of Talking to Strangers

by Henry D. Schlinger Jr.

This article describes publishing outside behavior analysis, letters to editors, and columns, as well as communicating outside the box with editors, authors, and journalists. Publishing can occur in a wide range of journals (e.g., Consciousness and Cognition), in-house publications of professional associations (e.g., Association for Psychological Science's Observer), general science publications (e.g., American Scientist, The Scientist), publications in service to professions (e.g., The Chronicle of Higher Education), general interest and specialized magazines (e.g., Atlantic Monthly, Skeptical Inquirer), and newspapers (e.g., Los Angeles Times). Communicating with editors, authors, and journalists includes, for instance, formal correspondence with editors and personal correspondence with authors and journalists outside the box about misunderstandings, commonalities, and complementarities of their work with respect to ours. The consequences of publishing and communicating are often unforeseen and fortuitous, many of which can never occur by remaining in the box.



Annales de Medicine Interne • 1990

# Failure of prevention of malaria by mefloquine in West Africa

Article in French and English

by Bricaire F1, Gay F, Caumes E, Datry A, Bustos D
Félix H, Paris L, Danis M, Gentilini M.

1Service des Maladies Infectieuses et Parasitaires
Centre Hospitalier Pitié-Salpêtrière, Paris

Mefloquine (Lariam) is extensively prescribed for the prevention of malaria in chloroquine-resistant areas. However, in west Africa, most of the strains of Plasmodium falciparum are still sensitive to chloroquine. In addition, a few of these strains are inherently resistant to mefloquine. Under these conditions, we must expect to see the failure of mefloquine prophylaxis in travellers returning from west Africa. We report here 5 such failures. The in vitro susceptibility of Plasmodium falciparum isolates from 4 of these patients was evaluated and showed that all 4 had normal sensitivity to chloroquine and quinine, 3 were resistant to mefloquine and one had reduced susceptibility to mefloquine. Mefloquine blood levels (measured 3 times) were within the normal protective range. These case reports indicate that mefloquine should be used cautiously for malaria prevention in west Africa. They also point out that, regardless of the prophylactic method used, fever in a traveller returning from endemic malaria regions always dictates the analysis of a thick blood smear to rule out the diagnosis of malaria.

https://www.ncbi.nlm.nih.gov/pubmed/2285203

***"... we must expect to see the failure of mefloquine prophylaxis in travellers returning from west Africa."***

*"... a suicide attempt by drowning."*

Therapie • September 1990

**Recurrent psychiatric manifestations during malaria prevention with mefloquine. A case report**

Article in French and English

by Rodor F1, Bianchi G, Grignon S, Samuelian JC, Jouglard J.

1Centre de Pharmacovigilance, Hôpital Salvator, Marseille

The authors report the case of a 22 years old woman without psychiatric antecedent who started a prophylaxis with mefloquine for a journey in a chloroquino resistant area. The first tablet induced an acute psychiatric syndrome which lasted five days; the second tablet induced the recidive of the psychiatric data and a suicide attempt by drowning.

https://www.ncbi.nlm.nih.gov/pubmed/2260038

Der Nervenarzt • May 1992

## Psychotic episode caused by prevention of malaria with mefloquine. A case report

Article in German and English

by Folkerts H1, Kuhs H.

1Klinik für Psychiatrie, Westfälischen Wilhelms-Universität Münster.

We report on a 41 year old woman, who after 750 mg mefloquine, a newer antimalarial agent, developed a psychosis with dizziness, confusion and delusions. The symptoms were more intensive and remained longer than hitherto reported in the literature. A total of 23 patients are known to have had psychiatric adverse effects under mefloquine. Psychotic episodes are undoubtedly though rarely associated with the intake of mefloquine.

https://www.ncbi.nlm.nih.gov/pubmed/1603191

This report from 1992 indicates that “undoubtedly” psychotic episodes are “rarely” associated with the use of Mefloquine. Yet as we move through time and we advance our medical knowledge of Mefloquine and how it actually works after years of painstaking research—as we come to understand the mechanisms of action—we’ll learn that far more people were and are affected by their use of Mefloquine merely because strict prescribing instructions simply weren’t followed in the majority of cases where Mefloquine is prescribed. The medical communities confidence in the drug and the manufacturers negligence has led to untold numbers of damaged people many of whom will never connect their symptoms and the pain they’re enduring to the use of the drug. Something the manufacturer relies on.

Tropical and Geographical Medicine • 1995

## Acute psychosis after mefloquine. Report of six cases

by Sowunmi A1, Adio RA, Oduola AM, Ogundahunsi OA, Salako LA.

Department of Pharmacology and Therapeutics, University of Ibadan, Nigeria

A self-limiting psychosis characterized by acute onset of visual and auditory hallucinations and poor sleep developed in six adults between 8 and 24 hours after oral administration of 750-1500 mg of the antimalarial mefloquine. All patients had no personal or family history of psychosis and were neurologically and mentally normal before mefloquine ingestion. These cases illustrate that acute psychotic symptoms may occur in patients treated with mefloquine.

https://www.ncbi.nlm.nih.gov/pubmed/8560592

**“These cases illustrate that acute psychotic symptoms may occur in patients treated with mefloquine”**

Der Nervenarzt • May 1996

# Psychopathological phenomena in long-term follow-up of acute psychosis after preventive mefloquinine (Lariam) administration

Article in German and English

by Meszaros K1, Kasper S.

1. Klinische Abteilung für Allgemeine Psychiatrie
Universitätsklinik für Psychiatrie, Wien

There are some reports about neuropsychiatric side effects associated with the intake of the antimalarial drug mefloquine. We report a long-term observation of a patient suffering for his first time on an acute psychosis under mefloquine prophylaxis. Mefloquine's role as a drug possibly inducing psychosis and the influence of vulnerability therefore will be discussed.

https://www.ncbi.nlm.nih.gov/pubmed/9005352

Harefuah • July 1999

## Neuropsychiatric side effects of malarial prophylaxis with mefloquine (Lariam)

Article in Hebrew and English

by T. Minei-Rachmilewitz

Department of Psychiatry, Hadassah Hospital Ein Karem
Jerusalem, Israel

There has been an increased incidence of malaria among Europeans returning from Africa and Asia. The relatively new antimalarial mefloquine (Lariam) has become extremely popular due to its efficacy in treating the wide-spread chloroquine-resistant Plasmodium falciparum. Mefloquine is used both for prophylaxis and treatment of malaria and is relatively well tolerated. However, since introduced in 1985, there have been over 100 reports of severe neurologic and psychiatric adverse effects associated with its use, including acute psychosis, affective disorders, acute confusional states and seizures. We describe a 39-year-old woman who developed acute psychosis after being given mefloquine prophylaxis. Adverse effects occur more often after therapeutic rather than prophylactic use, and those with a history of seizures or psychiatric illness are at increased risk of developing these reactions. Physicians should be aware of these possible side effects and prescribe mefloquine only when indicated.

https://www.ncbi.nlm.nih.gov/pubmed/10959270

# Army's Lariam expert funded by drug-maker

Mark Tighe

A PROFESSOR who has advised the Department of Defence on its practice of prescribing the Lariam anti-malarial drug to Irish troops has previously received research funding from Roche, its manufacturer.

Patricia Schlagenhauf, a pharmacist and editor of the Journal of Travel Medicine, states in her online CV that she has been the "malaria prevention adviser" to the "Irish armed forces" since 2010.

The Department of Defence confirmed that she contributed to its working-group report on the use of Lariam that Alan Shatter, the justice minister, has declined to publish on the basis of legal privilege.

The state is facing 24 High Court actions from current and former soldiers who claim they became ill after being prescribed Lariam.

An updated warning published by Roche last July said the drug, which is no longer used by the US Army, can cause "serious neuropsychiatric disorders". The most common of these include "abnormal dreams, insomnia, anxiety and depression". The warning also states the drug may cause serious mental health problems, including suicidal thoughts or self-endangering behaviour.

Schlagenhauf has published at least 12 research papers on the subject of travel medicine, in which she declares receiving financial support or consultancy fees from Roche.

Remington Nevin, an American researcher who believes soldiers should not use Lariam because of its side-effects, claimed it was inappropriate for the Irish Defence Forces to employ Schlagenhauf.

"The Irish government's hiring of a paid consultant to a drug company whose anti-malarial drug is clearly linked to suicide is akin to their hiring a tobacco company scientist to consult on cancer-prevention policies," Nevin said. He believes reports published by Schlagenhauf have understated the dangers posed by Lariam.

In a 2000 paper that she co-wrote, Schlagenhauf suggested travelling abroad could be causing mental problems for people taking anti-malarial drugs. "The precise role of antimalarial drugs in neuropsychiatric adverse events is difficult to define," the paper said. "Is travel a catalyst? Do troubled minds travel or does travel trouble minds?"

Schlagenhauf, who has dual Irish and Swiss citizenship, said she did not believe Roche's financial contribution to her research affected her independence. Such support is normal in medical research, she said.

"I don't get paid extra if a certain drug comes out on top," she added. "This type of research is not feasible

Continued on page 2 ▸▸

***"... since introduced in 1985, there have been over 100 reports of severe neurologic and psychiatric adverse effects associated with its use ..."***

La Clinica Terapeutica • September 1999

## Mefloquine and ototoxicity: a report of 3 cases

Article in Italian and English

by Fusetti M1, Eibenstein A, Corridore V, Hueck S, Chiti-Batelli S.

1. Dipartimento Discipline Chirurgiche, Università dell'Aquila, Italia

We report these cases of high-frequency sensorineural hearing loss and tinnitus, following malaria prophylaxis with mefloquine (Lariam). Only one patient had partial remission of hearing loss after suspension of the treatment. In the remaining two cases the symptomatology remained unchanged. None of the patients reported improvement of tinnitus. Our experience suggests that a routine audiologic evaluation, before and after prophylactic use of antimalarial drugs, is important to monitor potential hearing deficit.

https://www.ncbi.nlm.nih.gov/pubmed/10687269

Psychiatrische Praxis • September 1999

## Acute paranoid hallucinatory psychosis following mefloquine prophylaxis (Lariam)

Article in German and English

by Krüger E1, Grube M, Hartwich P.

1Klinik für Psychiatrie und Psychotherapie der Städtischen Kliniken, Frankfurt A.M.

Mefloquine is a drug of choice for malaria prophylaxis in Africa because of the spread of chloroquine resistant plasmodium falciparum. On the other hand there are some reports about severe neuropsychiatric side effects associated with the intake of mefloquine medication. In our paper we present a case-report of a patient suffering for the first time from an acute paranoid psychosis induced by mefloquine prophylaxis.

https://www.ncbi.nlm.nih.gov/pubmed/10535096

The Journal Of Travel Medicine • 2001

## Malaria Antibodies and Mefloquine Levels among United Nations Troops in Angola

by Eli Schwartz, Florian Paul, Hedva Pener, Shlomo Almog, Michal Rotenberg, and Jacob Golenser

The Center for Geographical Medicine, Sheba Medical Center, Tel-Hashomer, Israel
UNAVEM III, Angola
The Israeli Ministry of Health, Jerusalem, Israel
The Laboratory of Clinical Pharmacology and Toxicology
Sheba Medical Center, Tel-Hashomer, Israel
The Kuvin Center for Tropical and Infectious Diseases
The Hebrew University - Hadassah Medical School, Jerusalem, Israel

**Background**: The United Nations deployed about 8,000 soldiers in a peacekeeping mission in Angola. Malaria is the most common disease there and consequently it was the major risk to the UN troops. Most of them are from malaria free areas. As a result of improper prophylactic measures there were many cases of malaria, including some deaths in 1995. In February–March 1996, an Israeli team was sent to Angola to evaluate the malaria situation among UN soldiers. This paper deals specifically with some aspects of chemoprophylaxis and diagnosis. The efforts were concentrated in one particular area where malaria incidence had been reported as the highest.
**Methods**: Blood samples were collected from nonimmune soldiers who were using mefloquine as a prophylactic drug and were exposed to malaria. The mefloquine and the antimalarial antibody plasma levels were monitored.
**Results**: While the local laboratory indicated that about 80% had a malaria episode, the serological results revealed that only 5 soldiers of the 56 (9%) examined had antimalarial antibodies, of which 3 were Angolans. Despite a controlled prophylactic regimen there was considerable variability in mefloquine plasma levels: 46% of the samples were below the required prophylactic level and 26% above it. All patients who were proven positive with malaria by both microscopic and serologic observation had a low level of mefloquine.
**Conclusions**: In field conditions, a kit which identifies plasmodial antigens, is preferable, to a microscopic diagnostic method. Controlled mefloquine prophylaxis may not prevent malaria, especially when blood levels are low. The reason for the low mefloquine blood levels is not clear and needs further evaluation.

**THE ASSISTANT SECRETARY OF DEFENSE**

1200 DEFENSE PENTAGON
WASHINGTON, DC 20301-1200

AUG 12 2013

HEALTH AFFAIRS

MEMORANDUM FOR ASSISTANT SECRETARY OF THE ARMY (MANPOWER AND RESEREVE AFFAIRS)
ASSISTANT SECRETARY OF THE NAVY (MANPOWER AND RESERVE AFFAIRS)
ASSISTANT SECRETARY OF THE AIR FORCE (MANPOWER AND RESERVE AFFAIRS
COMMANDER, JOINT TASK FORCE, NATIONAL CAPITAL REGION-MEDICAL

SUBJECT: Notification for Healthcare Providers of Mefloquine Box Warning

On July 29, 2013, the Food and Drug Administration (FDA) issued a labeling change for mefloquine requiring a boxed warning for the medication. The attached FDA Drug Safety Communication includes strengthened and updated warnings due to potential neurologic and psychiatric side effects associated with mefloquine. This FDA notice focuses on warnings in the prescribing information, but does not change the indications for the medication.

The updated (April 15, 2013) Department of Defense (DoD) Guidance on Medications for Prophylaxis of Malaria reiterates that mefloquine should be reserved for individuals who cannot take the first-line medications, and reinforces the need to evaluate each patient for contraindications before starting mefloquine. As a result of DoD guidance limiting its use, the number of active duty Service members who received prescriptions for mefloquine decreased from 17,361 in 2008, to 889 through July 2013. Use in other DoD beneficiaries has also decreased dramatically.

**DoD Mefloquine Prescriptions**
**2008 – July 2013**

| Year | # of Prescriptions | # of Individuals | # of Active Duty |
|---|---|---|---|
| 2008 | 23,889 | 21,628 | 17,361 |
| 2009 | 21,856 | 20,041 | 16,272 |
| 2010 | 14,374 | 13,295 | 9,764 |
| 2011 | 7,896 | 7,040 | 3,836 |
| 2012 | 5,370 | 4,768 | 2,040 |
| 2013 (7 Months) | 2,618 | 2,417 | 889 |

It is critical that all DoD healthcare providers continue to prescribe mefloquine in accordance with the FDA requirements and the DoD guidance. Mefloquine is the drug of last resort for malaria prophylaxis and should only be used in persons with contraindications to chloroquine, doxycycline and atovaquone-proguanil. Mefloquine should be used with caution in

Papua and New Guinea Medical Journal • September 2002

## Paranoid psychosis related to mefloquine antimalarial prophylaxis

by Fuller SJ1, Naraqi S, Gilessi G.

1. Sydney University Department of Medicine, Nepean Hospital, Australia

Mefloquine is an important antimalarial drug for treatment and prophylaxis of chloroquine-resistant malaria. Its use has been associated with neuropsychiatric side-effects. We report a case of paranoid psychosis associated with mefloquine occurring in a remote part of Papua New Guinea. Adverse reactions and contraindications are discussed. This case underlines the importance of awareness of neuropsychiatric side-effects with mefloquine use and of taking a careful psychiatric history before prescribing mefloquine.

https://www.ncbi.nlm.nih.gov/pubmed/12968793

***"We report a case of paranoid psychosis associated with mefloquine ..."***

Malaria Journal • June 2003

# The acute neurotoxicity of mefloquine may be mediated through a disruption of calcium homeostasis and ER function in vitro

by Geoffrey S Dow*1, Thomas H Hudson1
Maryanne Vahey2 and Michael L Koenig3

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3. Division of Neuroscience, Walter Reed Army Institute of Research
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**Background**: There is no established biochemical basis for the neurotoxicity of mefloquine. We investigated the possibility that the acute in vitro neurotoxicity of mefloquine might be mediated through a disruptive effect of the drug on endoplasmic reticulum (ER) calcium homeostasis.

**Methods**: Laser scanning confocal microscopy was employed to monitor real-time changes in basal intracellular calcium concentrations in embryonic rat neurons in response to mefloquine and thapsigargin (a known inhibitor of the ER calcium pump) in the presence and absence of external calcium. Changes in the transcriptional regulation of known ER stress response genes in neurons by mefloquine were investigated using Affymetrix arrays. The MTT assay was employed to measure the acute neurotoxicity of mefloquine and its antagonisation by thapsigargin.

**Results**: At physiologically relevant concentrations mefloquine was found to mobilize neuronal ER calcium stores and antagonize the pharmacological action of thapsigargin, a specific inhibitor of the ER calcium pump. Mefloquine also induced a sustained influx of extra-neuronal calcium via an unknown mechanism. The transcription of key ER proteins including GADD153, PERK, GRP78, PDI, GRP94 and calreticulin were up-regulated by mefloquine, suggesting that the drug induced an ER stress response. These effects appear to be related, in terms of dose effect and kinetics of action, to the acute neurotoxicity of the drug in vitro.

**Conclusions**: Mefloquine was found to disrupt neuronal calcium homeostasis and induce an ER stress response at physiologically relevant concentrations, effects that may contribute, at least in part, to the neurotoxicity of the drug in vitro.

Orvosi Hetilap • January 2005

# Neuropsychiatric symptoms caused by mefloquine (report of several cases)

Article in Hungarian and English

by Murai Z1, Baran B, Tolna J, Szily E, Gazdag G.

1. Semmelweis Egyetem, Általános Orvostudományi Kar
Pszichiátriai és Pszichoterápiás Klinika, Budapest

**INTRODUCTION**: The number of Hungarian citizens travelling to countries infected with malaria is increasing year by year. Mefloquine is the most effective medicine in the prophylaxis and treatment of malaria. However, neuropsychiatric side-effects can more often be seen with the use of mefloquine compared to other anti-malaria drugs.

**AIMS**: To assess the neuropsychiatric side-effects with mefloquine prophylaxis; to screen those patients who are possibly affected by the side-effects and to explore factors that forecast the possible side-effects.

**METHOD**: The retrospective analysis of patients, who in the past 2 years, have had mefloquine prophylaxis and then turned up at Semmelweis University, Department of Psychiatry and Psychotherapy and at Szent László Hospital, Outpatient Department of Psychiatry and Addictology because of neuropsychiatric symptoms.

**RESULTS**: Out of the 6 cases presented, whose neuropsychiatric symptoms ranged from slight dizziness, malaise through panic attacks and depression to psychosis, the preceeding psychiatric condition was positive in 4 cases. Even the most serious psychiatric symptoms disappeared within a few days using temporary drug-treatment. In those cases in whom the side-effects were more serious, a positive psychiatric history or a more sensitive personality differing from the average was established.

**CONCLUSIONS**: Because of the low number of cases it is not possible to draw a general conclusion. After analysis of the data the authors assume, that besides the psychiatric history, the premorbid personality can also be a factor that forecasts the possible neuropsychiatric side-effects caused by mefloquine prophylaxis.

https://www.ncbi.nlm.nih.gov/pubmed/15693445

Malaria Journal • August 2006

# Psychosis with paranoid delusions after a therapeutic dose of mefloquine: a case report

by Tuan M Tran*1, Joseph Browning2 and Mary L Dell2

1. Emory University School of Medicine, Emory University, Atlanta GA 30322, USA
2. Department of Psychiatry, Emory University School of Medicine, Atlanta, GA 30322, USA
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**Background**: Convenient once-a-week dosing has made mefloquine a popular choice as malaria prophylaxis for travel to countries with chloroquine-resistant malaria. However, the increased use of mefloquine over the past decade has resulted in reports of rare, but severe, neuropsychiatric adverse reactions, such as anxiety, depression, hallucinations and psychosis. A direct causality between mefloquine and severe reactions among travelers has been partly confounded by factors associated with foreign travel and, in the case of therapeutic doses of mefloquine, the central nervous system manifestations of Plasmodium infection itself. The present case provides a unique natural history of mefloquine-induced neuropsychiatric toxicity and revisits its dose-dependent nature.

**Case presentation**: This report describes an acute exacerbation of neuropsychiatric symptoms after an unwarranted therapeutic dose (1250 mg) of mefloquine in a 37-year-old male previously on a once-a-week prophylactic regimen. Neuropsychiatric symptoms began as dizziness and insomnia of several days duration, which was followed by one week of escalating anxiety and subtle alterations in behaviour. The patient's anxiety culminated into a panic episode with profound sympathetic activation. One week later, he was hospitalized after developing frank psychosis with psychomotor agitation and paranoid delusions. His psychosis remitted with low-dose quetiapine.

**Conclusion**: This report suggests that an overt mefloquine-induced psychosis can be preceded by a prodromal phase of moderate symptoms such as dizziness, insomnia, and generalized anxiety. It is important that physicians advise patients taking mefloquine prophylaxis and their relatives to recognize such symptoms, especially when they are accompanied by abrupt, but subtle, changes in behaviour. Patients with a history of psychiatric illness, however minor, may be at increased risk for a mefloquine-induced neuropsychiatric toxicity. Physicians must explicitly caution patients not to self-medicate with a therapeutic course of mefloquine when a malaria diagnosis has not been confirmed.

*"Serious neurologic and psychiatric adverse events associated with mefloquine have been reported since its introduction in 1985."*

Presse Medicale • May 2006

## Spectacular suicide associated with mefloquine

Article in French and English

Jousset N1, Guilleux M, de Gentile L, Le Bouil A, Turcant A, Rougé-Maillart C.

1Service de médecine légale, CHU d'Angers-49
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We present a case in which suicide was a severe neuropsychiatric reaction to treatment with mefloquine. Physicians must be aware of these serious psychiatric complications and bear them in mind when faced with atypical behavior or suspected suicide.

**CASE REPORT:**

The body of a 27-year-old man was discovered at his home, covered with multiple knife wounds. The autopsy report concluded that death was due to a craniocerebral wound from a violent blow. Homicide was initially suspected. Suicide during acute psychosis associated with mefloquine was suggested, and toxicologic analyses confirmed this hypothesis.

**DISCUSSION:**

Serious neurologic and psychiatric adverse events associated with mefloquine (Lariam) have been reported since its introduction in 1985. Mefloquine prophylaxis is recommended for travelers to high-risk areas of chloroquine-resistant plasmodium falciparum. The risk of malarial infection and the proven efficacy of mefloquine to prevent malaria should be weighed against the risk of drug-associated adverse events. Physicians must nonetheless be aware of these serious psychiatric complications, especially when faced with atypical behavior and atypical suicides. The patient's' family and friends should be asked about a possible trips abroad that might have entailed antimalaria treatment, even several months earlier. Testing for mefloquine during toxicological examinations is then essential. The World Health Organization recommendations and contraindications must be followed in prescribing mefloquine.

https://www.ncbi.nlm.nih.gov/pubmed/16710147

*"... suicide was a severe neuropsychiatric reaction to treatment with mefloquine."*

The report on the previous page shows that by 2006 we were able to diagnose death as the result of Lariam on autopsy assuming we suspected and knew to test for it. This is significant since death by Larium could now be laboratory confirmed while somehow the denial remained constant even in our courts of law.

Malaria Journal • February 2008

# Prevalence of contraindications to mefloquine use among USA military personnel deployed to Afghanistan

by Remington L Nevin*1, Paul P Pietrusiak2 and Jennifer B Caci3

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**Background**: Mefloquine has historically been considered safe and well-tolerated for long-term malaria chemoprophylaxis, but its prescribing requires careful attention to rule out contraindications to its use, including a history of certain psychiatric and neurological disorders. The prevalence of these disorders has not been defined in cohorts of U.S. military personnel deployed to areas where long-term malaria chemoprophylaxis is indicated.

**Methods**: Military medical surveillance and pharmacosurveillance databases were utilized to identify contraindications to mefloquine use among a cohort of 11,725 active duty U.S. military personnel recently deployed to Afghanistan.

**Results**: A total of 9.6% of the cohort had evidence of a contraindication. Females were more than twice as likely as males to have a contraindication (OR = 2.48, P < 0.001).

**Conclusion**: These findings underscore the importance of proper systematic screening prior to prescribing and dispensing mefloquine, and the need to provide alternatives to mefloquine suitable for long-term administration among deployed U.S. military personnel.

***"The prevalence of these disorders has not been defined in cohorts of U.S. military personnel deployed to areas where long-term malaria chemoprophylaxis is indicated."***

The Cochrane Collaboration • 2009

## Drugs for preventing malaria in travellers (Review)

by FA Jacquerioz and AM Croft

Plain Language Summary

Malaria is a mosquito-transmitted disease which commonly infects international travellers, sometimes fatally. Deaths from malaria are usually caused by Plasmodium falciparum. Malaria can be prevented through a range of anti-mosquito precautions (barrier measures), and by taking antimalaria drugs (chemoprophylaxis).

Chloroquine is effective chemoprophylaxis in those parts of the world where P. falciparum has not developed resistance to chloroquine. For most malaria-endemic regions, however, travellers must take a newer and stronger drug regimen. These newer antimalaria regimens have unpredictable adverse effects, including severe illness or death.

This review was designed to assess the efficacy, safety, and tolerability of atovaquone-proguanil, doxycycline, and mefloquine (the three currently available chemoprophylaxis choices for regions with P. falciparumresistance) compared to each other, and also when compared to chloroquine-proguanil (an older drug combination) and to primaquine (a candidate for chemoprophylaxis).

We found eight trials (4240 participants). Overall the evidence base was small, and we found no evidence to support the use of primaquine. There was only limited evidence on which of the three currently available drugs is most effective in preventing malaria. While none of the eight trials reported any serious adverse events (which are usually rare) all trials reported common adverse events from antimalaria drugs.

Atovaquone-proguanil and doxycycline are well tolerated by most travellers, and they are less likely than mefloquine to cause neuropsychiatric adverse events. Chloroquine-proguanil causes more gastrointestinal adverse events than other chemoprophylaxis. In other respects, the common unwanted effects of currently available drugs are similar.

As well as the eight trials, we also found 22 published case reports of deaths, including five suicides, associated with mefloquine use at normal dosages. No other currently used drugs were reported as causing death, at normal dosages.

In conclusion, there were differences in the common unwanted effects of the drugs which are currently available to prevent malaria, in adult and child travellers. However, the quality of evidence was overall low. Atovaquone-proguanil and doxycycline are the best tolerated regimens. Mefloquine has more adverse effects than other drugs, and these adverse effects are sometimes serious. However mefloquine may still be an appropriate choice for those travellers who have taken it previously, without any adverse events. Other factors should be considered by prescribers, in addition to tolerability: cost, ease of administration, possible drug-drug interactions, travel itinerary, and the additional protection that may be afforded by doxycycline against other infections, besides malaria.

**"Mefloquine has more adverse effects than other drugs, and these adverse effects are sometimes serious."**

Journal of Child Neurology • August 2009

# Childhood Mefloquine-Induced Mania and Psychosis: A Case Report

by Rajoo Thapa, MD, and Biswajit Biswas, MD

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An 11-year-old girl presented with features of mania and psychosis of 4 days' duration. The mother noticed that her child became increasingly talkative and irritable, which she first noticed about 10 days prior to presentation. Concomitantly, she noted that the patient slept for fewer hours and spent more time wandering about in the streets. She also received complaints of the patient's inappropriate behavior in the form of physical violence and foul and provocative utterances in the neighborhood. Over the last 4 days, the girl developed increasing mania and hallucinations to the point of psychosis. She talked about herself being an all-powerful goddess responsible for wiping out evils from the face of the earth and that "demons" were all out to get her. She believed that her friends and all those around her were destined to serve her, but at times became suspicious that they would in reality, harm her. At times, she would tell her mother that she could hear voices of the supreme deities, commanding her to fetch the heads of "bad people" and "troublemakers." Over the last 2 days, she ate little, believing she had supreme powers that could keep her alive and healthy without food. There were several other instances of delusions of reference, grandeur, and persecution.

The American Journal
of Forensic Medicine and Pathology • December 2010

# Suicide by Skull Stab Wounds
# A Case of Drug-Induced Psychosis

Nathalie Jousset, MD,* Clotilde Rouge´-Maillart, MD,*Þ
Alain Turcant, MD,þ Michel Guilleux, MD,*
Anne Le Bouil, MD,þ and Antoine Tracqui, MD§

Suicide by stabbing to the head and/or driving sharp objects into the skull is of extreme rarity. This article reports the case of a 27-year-old man, who committed suicide by multiple knife stabs and cuts to the head, the torso, one shoulder and the forearms. Autopsy showed a perforating wound of the skull and the 10-cm long broken blade of the knife being still embedded in the right temporal lobe of the brain. The deceased had no history of psychiatric illness but was currently treated bymefloquine, a quinine derivative associated with a high rate of psychiatric adverse effects. Toxicological examination confirmed a recent intake of mefloquine together with chloroquine, another antimalarial drug. To our knowledge, this is the first report of a completed suicide with very strong evidence of mefloquine implication. Discussion focuses upon mefloquine-induced psychiatric disorders and highlights the importance of performing toxicological investigations in cases of unusual suicides.

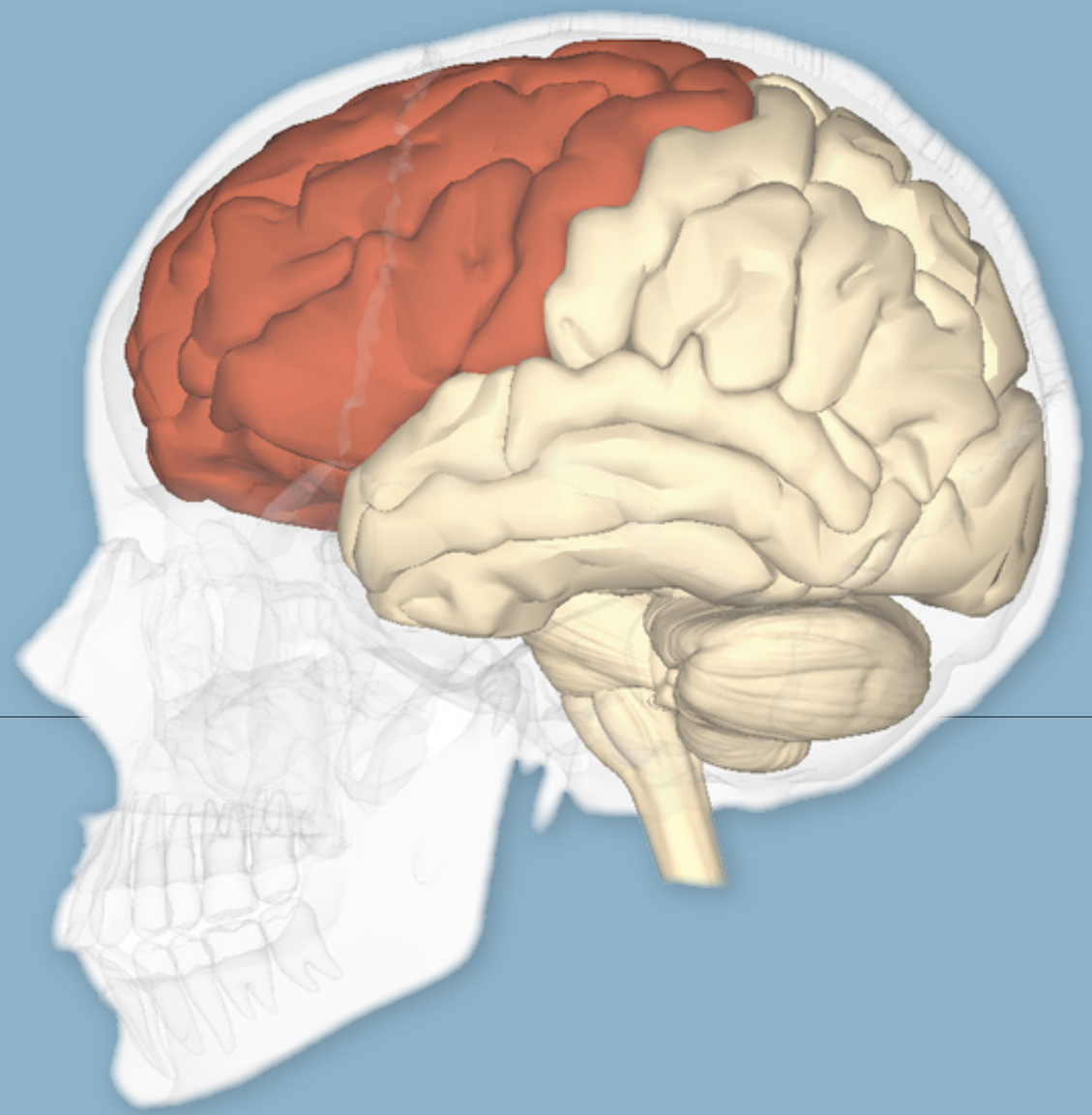

**FIGURE 1.** Body in the flat.

**FIGURE 3.** Stab wounds in the right temple.

**FIGURE 2.** Cross-shaped incision at the anterior side of the left forearm and wrist.

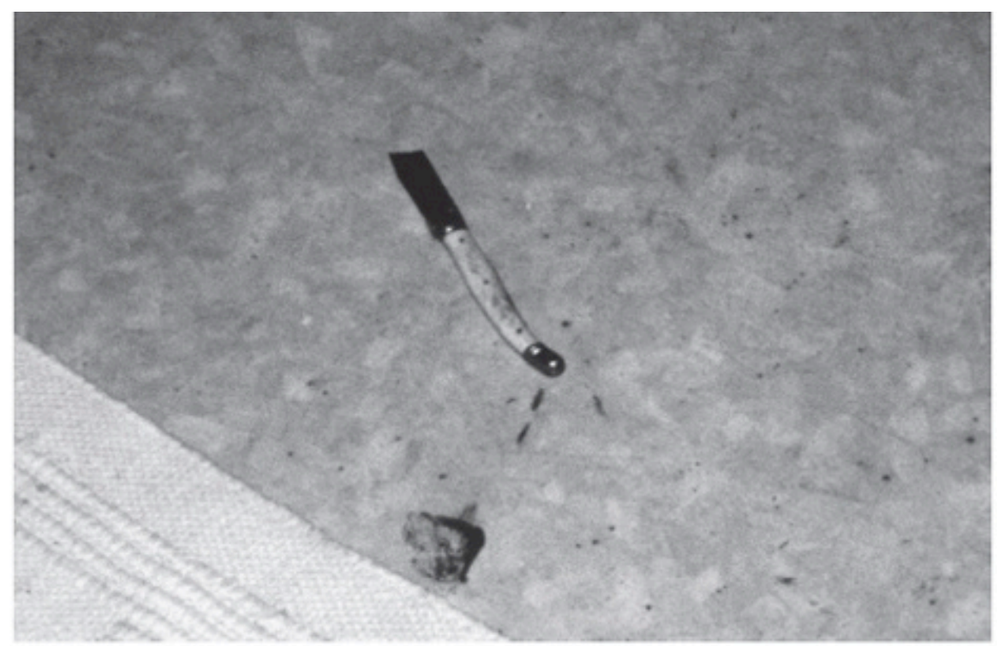

**FIGURE 4.** Kitchen knife with blade broken.

Seton Hall University School of Law
Center for Policy & Research

# DRUG ABUSE

## An exploration of the government's use of mefloquine at Guantanamo

December 2010

**Mark Denbeaux**
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Director, Seton Hall Law Center for Policy & Research
Counsel to Guantanamo detainees

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**Meghan Chrisner, Chrystal Loyer**
**Kelli Stout, Paul Taylor**
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**Marisa Hourdajian, Marissa Litwin, Katie Nadbielny,**
**Amy Sieminski, Nick Stratton, Philip Taylor, Lauren Winchester**
Contributors & Research Fellows

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Center for Policy & Research
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This Report demonstrates that the U.S. military routinely administered doses of mefloquine to detainees upon their arrival at GTMO without medical justification: 1250 mg of mefloquine was given to all detainees as a standard measure during inprocessing. Mefloquine is used for treatment of malaria only in mild to moderate cases of infection with the p. vivax or p. falciparum parasite. At GTMO, mefloquine was given to detainees before testing them for malaria, without regard for whether the detainee actually had malaria at all, let alone whether he carried one of the parasites treatable by mefloquine.

The standard of care rejects administering mefloquine to persons with a history of mental illness or a family history of mental illness, due to a greatly increased risk of severe adverse side effects for such persons. At GTMO, mefloquine was given to detainees without regard to prior mental health history or family mental health history.

This Report further demonstrates that the U.S. military knew, and any competent medical professional would have known, of the severe side effects caused by mefloquine: Mefloquine was first developed by the United States military. Mefloquine is a quinolone, a drug family the CIA experimented with under a project called MKULTRA that studied psychotropic drugs for behavioral modification for use as a weapon and interrogation tool.

As of 2002, Roche USA, the manufacturer of mefloquine under the brand name Lariam, warned of its contraindications and at least some of its severe side effects on the drug's package insert. Beginning at least as early as 1990, multiple peer-reviewed medical studies documented the severe adverse effects associated with mefloquine.

While it is impossible to make definitive conclusions as to the purposes for this policy without additional information, particularly detainee medical records, the available evidence may support one of several possible conclusions:

Gross medical malpractice: If government intended this mefloquine regime for malaria treatment and control, it was done in a manner that jeopardized the health and perhaps the lives of the detainees and that violated basic standards of medical care. Mefloquine was given in order to bring about the adverse effects for one of three reasons. Any of these would likely satisfy the legal definition of torture as articulated by the Department of Justice in 2002.

- As part of a program of enhanced interrogation, the psychotropic effects of mefloquine may have been intended as an aid to breaking a detainee's resistance. This would be the psychological equivalent of waterboarding.
- As part of an experimental study to gather data on the side effects of mefloquine.
- As a punitive measure.

HEALTH RECORD | CHRONOLOGICAL RECORD OF MEDICAL CARE

DATE | SYMPTOMS, DIAGNOSIS, TREATMENT, TREATING ORGANIZATION (Sign each page)
JTF – 160, Medical Department, Guantanamo Bay, Cuba 09593

9/13/02

STANDARD INPROCESSING ORDERS FOR DETAINEES:

1. Mefloquine 750 mg PO now, 500 mg PO in 12 hours
2. Albendazole 400mg PO once
3. Chest X-ray: PA
4. LABS:

| | |
|---|---|
| | Hep A IgM |
| Hep B surface antigen/antibody | G6PD |
| Hep C - total | Serum (draw 2 extra red tops) |
| HIV | Hep B core antibody |
| Malaria Smear and PCR | |

Circle if indicated:

1. AFB Smear QAM x 3
2. Td .5ml IM once
3. Tetanus IG 250 Units IM once
4. PPD – read in 48 to 72 hours
5. Additional Orders:

Consults:

Needs reading glasses? Y or N
Optometry
General Surgery
Orthopedic Surgery
Dental

UA in am – ordered (b)(3):10 USC §130b.(b)
Zantac 150 mg po bid – ordered (b)(3):10 USC §130b.(b)

(b)(3):10 USC §130b.(b)(6)

Staff Signature:

Signature: (b)(3):10 USC §130b

(Medical Officer or Independent Duty Corpsman)

PATIENT'S IDENTIFICATION (Use this space for Mechanical Imprint) Typed Name in lieu of STANDARD FORM 600
NAME:
SSN: 888-00-0613
STATUS:
DOB:

GTMO JMG 18

HEALTH RECORD | CHRONOLOGICAL RECORD OF MEDICAL CARE

DATE | SYMPTOMS, DIAGNOSIS, TREATMENT, TREATING ORGANIZATION (Sign each page)
JTF – 160, Medical Department, Guantanamo Bay, Cuba 09593

STANDARD INPROCESSING ORDERS FOR DETAINEES:

1. Mefloquine 750 mg PO now, 500 mg PO in 12 hours
2. Albendazole 400mg PO once
3. Chest X-ray: PA
4. LABS:

| | |
|---|---|
| | Hep A IgM |
| Hep B surface antigen/antibody | G6PD |
| Hep C - total | Serum (draw 2 extra red tops) |
| HIV | Hep B core antibody |
| Malaria Smear and PCR | |

Circle if indicated:

1. AFB Smear QAM x 3
2. Td .5ml IM once
3. Tetanus IG 250 Units IM once
4. PPD – read in 48 to 72 hours
5. Additional Orders:

Consults:

Needs reading glasses? Y or N
Optometry
General Surgery
Orthopedic Surgery
Dental

Intuniv 1mg qd

Staff Signature: (b)(3):S(1)

Signature:

(Medical Officer or Independent Duty Corpsman)

PATIENT'S IDENTIFICATION (Use this space for Mechanical Imprint) Typed Name in lieu of STANDARD FORM 600
NAME:
SSN: D,JTF 000760
STATUS:
DOB: 888 00 0760

Slahi v. DoD (No. 06-CV-0597) - 3

| HEALTH RECORD | CHRONOLOGICAL RECORD OF MEDICAL CARE |
|---|---|
| DATE | SYMPTOMS, DIAGNOSIS, TREATMENT, TREATING ORGANIZATION (Sign each page) |
| 4/13/02 | JTF –160, Medical Department, Guantanamo Bay, Cuba 09560 |

**STANDARD INPROCESSING ORDERS FOR DETAINEES:**

1. Mefloquine 750 mg PO now, 500 mg PO in 12 hours
2. Albendazole 400mg PO once
3. Chest X-ray: PA
4. LABS:

| | |
|---|---|
| | Hep A IgM |
| Hep B surface antigen/antibody | G6PD |
| Hep C - total | Serum (draw 2 extra red tops) |
| HIV | Hep B core antibody |
| Malaria Smear and PCR | |

| Circle if indicated: | | Consults: |
|---|---|---|
| 1. | AFB Smear QAM x 3 | Needs reading glasses? Y or N |
| 2. | Td .5ml IM once | Optometry<br>General Surgery |
| 3. | Tetanus IG 250 Units IM once | Orthopedic Surgery |
| 4. | PPD – read in 48 to 72 hours | Dental |

Case Reports In Psychiatry • July 2011

# Severe Neuropsychiatric Reaction in a Deployed Military Member after Prophylactic Mefloquine

by Alan L. Peterson,1 Robert A. Seegmiller,2 and Libby S. Schindler2

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Recent studies of military personnel who have deployed to Iraq and Afghanistan have reported a number of combat-related psychiatric disorders such as post traumatic stress disorder, depression, and traumatic brain injury. This case report involves a 27-year-old male active-duty US military service member who developed severe depression, psychotic hallucinations, and neuropsychological sequelae following the prophylactic use of the antimalarial medication mefloquine hydrochloride. The patient had a recent history of depression and was taking antidepressant medications at the time of his deployment to the Middle East. Psychiatrists and other health care providers should be aware of the possible neuropsychiatric side effects of mefloquine in deployed military personnel and should consider the use of other medications for malaria prophylaxis in those individuals who may be at increased risk for side effects.

*"This case report involves a 27-year-old male active duty US military service member who developed severe depression, psychotic hallucinations, and neuropsychological sequelae following the prophylactic use of the antimalarial medication mefloquine hydrochloride."*

Tropical Medicine and International Health • 2012

## Mass administration of the antimalarial drug mefloquine to Guantanamo detainees: a critical analysis

by Remington L. Nevin

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Ft. Polk, LA, USA

Recently, evidence has emerged from an unusual form of mass drug administration practised among detainees held at US Naval Station Guantanamo Bay, Cuba, ostensibly as a public health measure. Mefloquine, an antimalarial drug originally developed by the US military, whose use is associated with a range of severe neuropsychiatric adverse effects, was administered at treatment doses to detainees immediately upon their arrival at Guanta´namo, prior to laboratory testing for malaria and irrespective of symptoms of disease. In this analysis, the history of mefloquine's development is reviewed and the indications for its administration at treatment doses are discussed. The stated rationale for the use of mefloquine among Guanta´namo detainees is then evaluated in the context of accepted forms of population-based malaria control. It is concluded that there was no plausible public health indication for the use of mefloquine at Guanta´namo and that based on prevailing standards of care, the clinical indications for its use are decidedly unclear. This analysis suggests the troubling possibility that the use of mefloquine at Guanta´namo may have been motivated in part by knowledge of the drug's adverse effects, and points to a critical need for further investigation to resolve unanswered questions regarding the drug's potentially inappropriate use.

**The Military, the government, the Pharmaceutical Industry and the Research Community all know that Mefloquine causes severe psychiatric disorders and that this would be especially so in prisoners under the conditions they were and are being held under. There is NO MALARIA in Cuba. The mass administration of LARIAM to Guantanamo Prisoner's in Cuba can be seen as nothing less than TORTURE.**

American Journal Of Forensic Medicine • June 2012

# Hallucinations and Persecutory Delusions in Mefloquine-Associated Suicide

by Remington L. Nevin, MD, MPH

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To the Editor:

With interest, I read the article by Jousset et al describing the disturbing and spectacular suicide associated with mefloquine in the presence of chloroquine. Mefloquine may induce a dose-dependent psychosis among travelers notable for its stereotypical prodrome of affective disturbance and memory impairment and marked by pronounced auditory and visual hallucinations and persecutory delusions. Active hallucinations and delusions in schizophrenic states are known to increase the risk of suicide; whether these were present in the case presented by Jousset et al is not clear from the report, although the stunning description and photographs, particularly of a cross carved into the forearm of the deceased, are suggestive of the religious themes noted in numerous reports of mefloquine psychosis. The schizomimetic features of mefloquine psychosis closely resemble those of phencyclidine toxicity and antiYN-methyl-D-aspartate receptor encephalitis. Mefloquine appears to produce a similar limbic and subcortical encephalopathy to the latter, suggesting a shared pathophysiological mechanism. Although the former 2 conditions are associated with dysregulated dopamine release resulting from postsynaptic GABAergic interneuron inhibition from pathological N-methyl-D-aspartate receptor antagonism, in mefloquine psychosis, dopamine dysregulation resulting from pathological inhibition of interneuron electrical coupling produced by mefloquine blockade of connexin 36 gap junctions may be to blame. Direct evidence in animal models of mefloquine inhibition of electrical coupling with effects on GABAergic inhibition and subsequent dopaminergic tone has recently been demonstrated. Dysregulated dopamine release was first proposed as a mechanism of mefloquine psychosis over 5 years ago; however, definitive clinical investigation of the condition has been lacking. Predisposing factors to mefloquine psychosis remain unclear, although drug induced or genetically influenced pharmacokinetic heterogeneity contributing to elevated brain parenchymal concentrations may be implicated. Whether chloroquine exerts an inhibitory effect on mefloquine efflux from brain parenchyma or merely has an independent pharmacodynamic effect, as suggested from reports of psychosis more weakly associated with its isolated use, awaits further elucidation. In the interim, this case would appear to add to the evidence implicating mefloquine in the causal mechanism of suicide, particularly if psychological autopsy reveals evidence of hallucinations and persecutory delusions or the cardinal sign of memory impairment, a feature that among recent travelers exposed to the drug is virtually pathognomonic for the encephalopathy associated with mefloquine psychosis.

**Table 5. Countries with a Risk of Malaria[1]**

| | | |
|---|---|---|
| **AFRICA** | | |
| Angola | Equatorial Guinea | Niger |
| Benin | Eritrea[3] | Nigeria |
| Botswana[3] | Ethiopia[3] | Rwanda |
| Burkina Faso | Gabon | São Tomé and Príncipe |
| Burundi | Gambia, The | Senegal |
| Cameroon | Ghana | Sierra Leone |
| Cape Verde[2] | Guinea | Somalia |
| Central African Republic | Guinea-Bissau | South Africa[3] |
| Chad | Kenya[3] | Sudan |
| Comoros | Liberia | Swaziland |
| Congo | Madagascar | Tanzania |
| Côte d'Ivoire | Malawi | Togo |
| Democratic Republic of the Congo | Mali | Uganda |
| Djibouti | Mauritania | Zambia |
| | Mayotte | Zimbabwe |
| | Mozambique | |
| | Namibia | |
| **AMERICAS** | | |
| Argentina[3,4] | Dominican Republic[3,4] | Honduras[3,4] |
| Bahamas, The[3,4,5] | Ecuador[3] | Mexico[3,4] |
| Belize[3,4] | El Salvador[3,4] | Nicaragua[3,4] |
| Bolivia[3] | French Guiana[3] | Panama[3,6] |
| Brazil | Guatemala[3,4] | Paraguay[3,4] |
| Colombia[3] | Guyana[3] | Peru[3] |
| Costa Rica[3,4] | Haiti[4] | Suriname[3] |
| | | Venezuela[3] |
| **ASIA** | | |
| Afghanistan | Iran[3] | Saudi Arabia[3] |
| Armenia[3,4] | Iraq[3,4] | Sri Lanka |
| Azerbaijan[3,4] | Korea, North[4] | Tajikistan |
| Bangladesh[3] | Korea, South[3,4] | Thailand[3] |
| Bhutan[3] | Laos[3] | Timor-Leste (East Timor) |
| Cambodia[3] | Malaysia[3] | Turkey[3,4] |
| China[7] | Myanmar[3] | Uzbekistan[4] |
| Georgia[3,4] | Nepal[3] | Vietnam[3] |
| India | Pakistan | Yemen |
| Indonesia[3] | Philippines[3] | |
| **OCEANIA** | | |
| Papua New Guinea | Solomon Islands | Vanuatu |

1. Only includes countries for which prophylaxis is recommended. Regional variation in risk may exist within a country. More detailed information is available at www.cdc.gov/malaria and by phone for medical personnel from the Malaria Branch of the CDC at 770-488-7788.
2. Limited to Island of Saõ Tiago.
3. No malaria in major urban areas.
4. Chloroquine is the drug of choice for prophylaxis.
5. Only Great Exuma Island.
6. Chloroquine is recommended in Bocas del Toro province.
7. Chloroquine is recommended except in Hainan and Yunnan provinces.

Travel Medicine and Infectious Disease • 2012

## Limbic encephalopathy and central vestibulopathy caused by mefloquine: A case report

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Mefloquine is a 4-methanolquinoline anti-malarial that in recent years has fallen out of favor for use as chemoprophylaxis against infection with chloroquine-resistant Plasmodium falciparum malaria owing in part to growing concerns of side effects and potential neurotoxicity. Despite over 20 years of licensed use, the pathophysiological mechanisms underlying mefloquine's neuropsychiatric and physical side effects and the clinical significance of the drug's neurotoxicity have remained poorly understood. In this report, an adverse reaction to mefloquine chemoprophylaxis is described characterized by prodromal symptoms of anxiety with subsequent development of psychosis, short-term memory impairment, confusion and personality change accompanied by complaints of disequilibrium and vertigo, with objective findings of central vestibulopathy. It is posited that these effects represent an idiosyncratic neurotoxic syndrome of progressive limbic encephalopathy and multifocal brainstem injury caused by the drug. This case provides insights into the clinical significance of mefloquine neuronal gap junction blockade and neurotoxicity demonstrated in animal models, points to recommendations for the management of affected patients including diagnostic considerations and appropriate referrals, and highlights critical implications for the continued safe use of the medication.

**"DESPITE OVER 20 YEARS OF LICENSED USE, THE PATHOPHYSIOLOGICAL MECHANISMS UNDERLYING MEFLOQUINE'S NEUROPSYCHIATRIC AND PHYSICAL SIDE EFFECTS AND THE CLINICAL SIGNIFICANCE OF THE DRUG'S NEUROTOXICITY HAVE REMAINED POORLY UNDERSTOOD."**

Society of Biological Psychiatry • 2012

## Mefloquine Blockade of Connexin 36 and Connexin 43 Gap Junctions and Risk of Suicide

by Remington L. Nevin

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The author acknowledges the assistance of Cecelia Higginbotham of the Bayne-Jones Army Community Hospital Medical Library and the author reports no biomedical financial interests or potential conflicts of interest

To the Editor:

Iread with great interest the convincing archival report by Ernst et al. (1) describing significantly reduced expression of the gap junction protein connexin 43 (Cx43) in the dorsal lateral prefrontal cortex of suicide completers. Their report, although cautiously avoiding a claim of causation, prompts the important question of whether pharmacologic blockade of Cx43 gap junctions and those of other connexins including connexin 36 (Cx36),maybe associated with a comparable risk of suicide resulting from expected disruptions in gap junction intercellular communication. Such a finding would add to the large body of accumulating evidence implicating disordered gap junction function with alterations in behavior (2). Mefloquine, a quinine derivative antimalarial compound associated in the medical literature with often spectacular cases of suicide and suicide attempt (3,4) is known to effect a potent blockade of both Cx43 and Cx36 gap junctions (5). Within the past few years, mefloquine blockade of Cx36 gap junctions has emerged as a favored investigative technique in the neuroscience literature (6). Studies in animal models and limited studies in humans have provided critical insights into the role of mefloquine blockade of Cx36 gap junctions in modifying a host of behaviorally relevant processes in regions of the brain with significant Cx36 expression, including the reticular activating system (7,8), ventral tegmental area (9), hypothalamus (10), thalamus (11), hippocampus (12,13), and amygdala (14). In their report, Ernst et al. (1) highlighted the well-established association of mefloquine with temporary psychosis. The features of mefloquine psychosis (15) closely resemble those of phencyclidine and ketamine toxicity (16). Mefloquine also appears to produce a diffuse limbic and subcortical encephalopathy resembling that observed in anti-N-methyl-D-aspartate receptor encephalitis (17), marked by the cardinal symptom of memory impairment (18,19) and suggesting a related pathophysiologic mechanism.

# MILITARY ACTIVITY CHURNS UP THE GROUND, CREATING PERFECT BREEDING CONDITIONS AND MASSED TROOPS PROVIDE IDEAL MOSQUITO FEEDING GROUNDS...

Journal of the American Academy of Psychiatry and the Law • 2013

# Psychiatric side effects of mefloquine: applications to forensic psychiatry

by Ritchie EC1, Block J, Nevin RL.

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Mefloquine (previously marketed in the United States as Lariam®) is an antimalarial medication with potent psychotropic potential. Severe psychiatric side effects due to mefloquine intoxication are well documented, including anxiety, panic attacks, paranoia, persecutory delusions, dissociative psychosis, and anterograde amnesia. Exposure to the drug has been associated with acts of violence and suicide. In this article, we discuss the history of mefloquine use and describe plausible mechanisms of its psychotropic action. Mefloquine intoxication has not yet been successfully advanced in legal proceedings as a defense or as a mitigating factor, but it appears likely that it eventually will be. Considerations for the application of claims of mefloquine intoxication in forensic settings are discussed.

***"Severe psychiatric side effects due to mefloquine intoxication are well documented ..."***

***"Exposure ... has been associated with acts of violence and suicide."***

Journal of the Royal Naval Medical Service • 2014

## The adverse effects of mefloquine in deployed military personnel

by S. Adshead

**INTRODUCTION**: Mefloquine (Lariam®) is an effective anti-malarial prescribed to over 35 million travellers world-wide as chemoprophylaxis. However, it has been the subject of increased scrutiny and media attention due to its association with significant neuropsychiatric adverse events. Anecdotal evidence suggests that patient trust in the drug is waning.
**METHODS**: A prospective questionnaire-based cohort study of 150 deployed military personnel prescribed mefloquine as anti-malaria chemoprophylaxis. The primary study objective was to assess the rate of adverse reactions. In addition, an audit of mefloquine prescriptions and subsequent patient follow-up was conducted.
**RESULTS**: Among a cohort of 111 individuals taking mefloquine, 54% reported at least one adverse effect and 13% required a change in prescription to a second-line anti-malarial, due to significant side-effects. All females prescribed mefloquine reported at least one adverse reaction. There were two cases of clinically significant adverse reactions.
**CONCLUSIONS**: There was a higher rate of adverse events reported amongst deployed military personnel than has been reported among civilian patients. This may be partly due to the stressful environment in which deployed personnel operate.

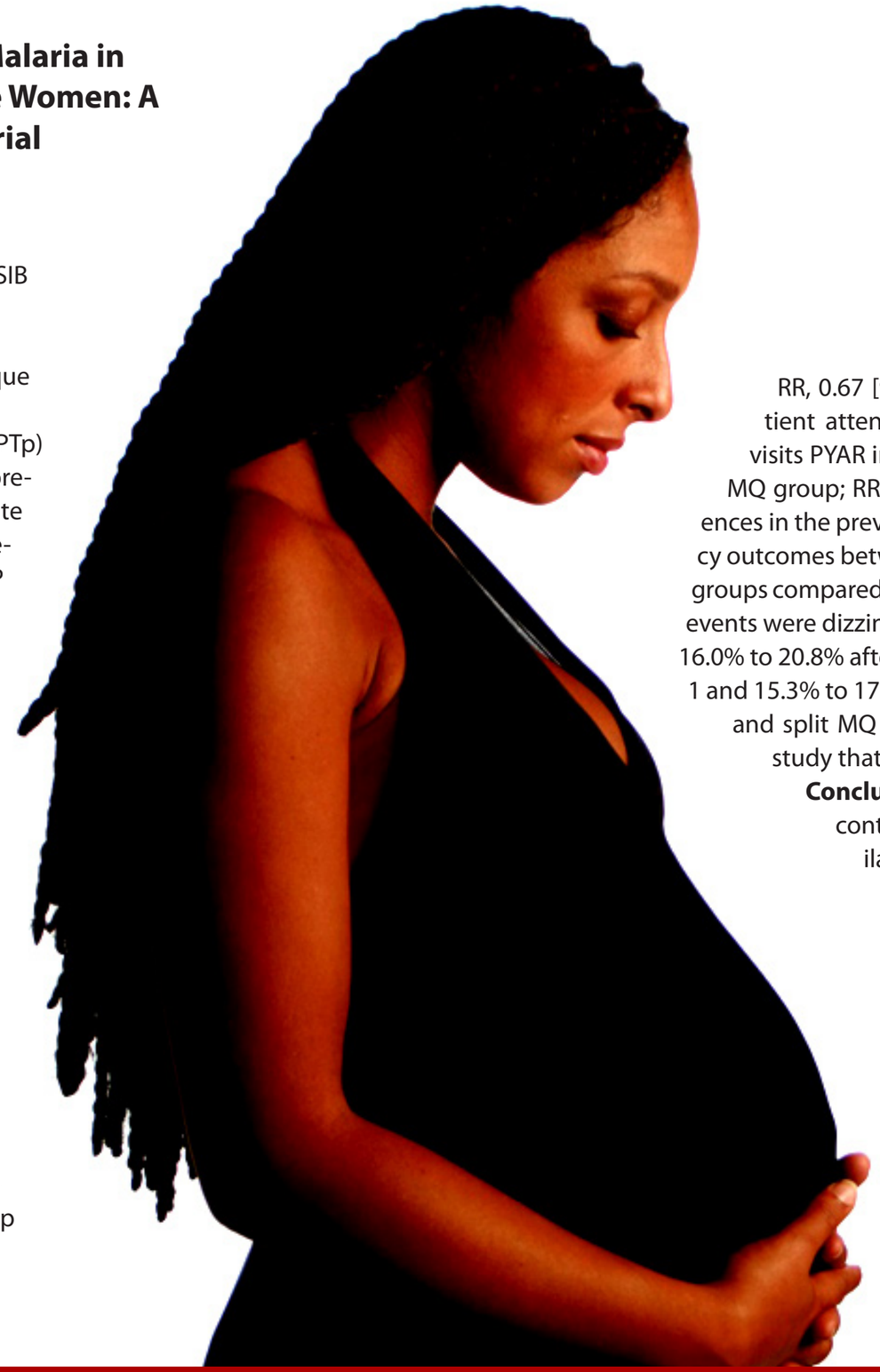
https://www.ncbi.nlm.nih.gov/pubmed/25895400

PLOS Medicine • September 2014

# Intermittent Preventive Treatment of Malaria in Pregnancy with Mefloquine in HIV-Negative Women: A Multicentre Randomized Controlled Trial

By Raquel Gonzalez, et al., 1, 2

1. Barcelona Centre for International Health Research (CRESIB Hospital Clı´nic-Universitat de Barcelona), ISGlobal Barcelona Institute for Global Health, Barcelona, Spain
2. Manhica Health Research Center (CISM), Manhica, Mozambique



**Background**: Intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine-pyrmethamine (SP) is recommended by WHO to prevent malaria in African pregnant women. The spread of SP parasite resistance has raised concerns regarding long-term use for IPT. Mefloquine (MQ) is the most promising of available alternatives to SP based on safety profile, long half-life, and high efficacy in Africa. We evaluated the safety and efficacy of MQ for IPTp compared to those of SP in HIVnegative women.

**Methods and Findings**: A total of 4,749 pregnant women were enrolled in an open-label randomized clinical trial conducted in Benin, Gabon, Mozambique, and Tanzania comparing two-dose MQ or SP for IPTp and MQ tolerability of two different regimens. The study arms were: (1) SP, (2) single dose MQ (15 mg/kg), and (3) split-dose MQ in the context of long lasting insecticide treated nets. There was no difference on low birth weight prevalence (primary study outcome) between groups (360/2,778 [13.0%]) for MQ group and 177/1,398 (12.7%) for SP group; risk ratio [RR], 1.02 (95% CI 0.86–1.22; p = 0.80 in the ITT analysis). Women receiving MQ had reduced risks of parasitemia (63/1,372 [4.6%] in the SP group and 88/2,737 [3.2%] in the MQ group; RR, 0.70 [95% CI 0.51–0.96]; p = 0.03) and anemia at delivery (609/1,380 [44.1%] in the SP group and 1,110/2743 [40.5%] in the MQ group; RR, 0.92 [95% CI 0.85–0.99]; p = 0.03), and reduced incidence of clinical malaria (96/ 551.8 malaria episodes person/year [PYAR] in the SP group and 130/1,103.2 episodes PYAR in the MQ group; RR, 0.67 [95% CI 0.52–0.88]; p = 0.004) and all-cause outpatient attendances during pregnancy (850/557.8 outpatients visits PYAR in the SP group and 1,480/1,110.1 visits PYAR in the MQ group; RR, 0.86 [0.78–0.95]; p = 0.003). There were no differences in the prevalence of placental infection and adverse pregnancy outcomes between groups. Tolerability was poorer in the two MQ groups compared to SP. The most frequently reported related adverse events were dizziness (ranging from 33.9% to 35.5% after dose 1; and 16.0% to 20.8% after dose 2) and vomiting (30.2% to 31.7%, after dose 1 and 15.3% to 17.4% after dose 2) with similar proportions in the full and split MQ arms. The open-label design is a limitation of the study that affects mainly the safety assessment.

**Conclusions**: Women taking MQ IPTp (15 mg/kg) in the context of long lasting insecticide treated nets had similar prevalence rates of low birth weight as those taking SP IPTp. MQ recipients had less clinical malaria than SP recipients, and the pregnancy outcomes and safety profile were similar. MQ had poorer tolerability even when splitting the dose over two days. These results do not support a change in the current IPTp policy.

Trial registration: ClinicalTrials.gov NCT 00811421
Pan African Clinical Trials Registry PACTR 2010020001429343

Journal of Parasitology Research • September 2015

# Malaria Prevention, Mefloquine Neurotoxicity, Neuropsychiatric Illness, and Risk-Benefit Analysis in the Australian Defence Force

by Stuart McCarthy

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The Australian Defence Force (ADF) has used mefloquine for malaria chemoprophylaxis since 1990. Mefloquine has been found to be a plausible cause of a chronic central nervous system toxicity syndrome and a confounding factor in the diagnosis of existing neuropsychiatric illnesses prevalent in theADF such as posttraumatic stress disorder and traumatic brain injury.Overall health risks appear to have been mitigated by restricting the drug's use; however serious risks were realised when significant numbers of ADF personnel were subjected to clinical trials involving the drug.The full extent of the exposure, health impacts for affected individuals, and consequences for ADF health management including mental health are not yet known, but mefloquine may have caused or aggravated neuropsychiatric illness in large numbers of patients who were subsequently misdiagnosed and mistreated or otherwise failed to receive proper care. Findings in relation to chronic mefloquine neurotoxicity were foreseeable, but this eventuality appears not to have been considered during risk-benefit analyses. Thorough analysis by the ADF would have identified this long-term risk as well as other qualitative risk factors. Historical exposure of ADF personnel to mefloquine neurotoxicity now also necessitates ongoing risk monitoring and management in the overall context of broader health policies.

Dedicated to Stuart McCarthy's late sister, Gabrielle McCarthy, a pioneer in the fight against HIV/AIDS.

# *We Want **YOU***
# *For Mefloquine Trials!*

Neuropharmacology • October 2015

## Mefloquine in the nucleus accumbens promotes social avoidance and anxiety-like behavior in mice

Mitra Heshmati, Sam A. Golden, Madeline L. Pfau, Daniel J. Christoffel
Elena L. Seeley, Michael E. Cahill, Lena A. Khibnik, Scott J. Russo*

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Mefloquine continues to be a key drug used for malaria chemoprophylaxis and treatment, despite reports of adverse events like depression and anxiety. It is unknown how mefloquine acts within the central nervous system to cause depression and anxiety or why some individuals are more vulnerable. We show that intraperitoneal injection of mefloquine in mice, when coupled to subthreshold social defeat stress, is sufficient to produce depression-like social avoidance behavior. Direct infusion of mefloquine into the nucleus accumbens (NAc), a key brain reward region, increased stress-induced social avoidance and anxiety behavior. In contrast, infusion into the ventral hippocampus had no effect. Whole cell recordings from NAc medium spiny neurons indicated that mefloquine application increases the frequency of spontaneous excitatory postsynaptic currents, a synaptic adaptation that we have previously shown to be associated with increased susceptibility to social defeat stress. Together, these data demonstrate a role for the NAc in mefloquine-induced depression and anxiety-like behaviors.

Journal Of Parasitology Research • October 2015

# Rational Risk-Benefit Decision-Making in the Setting of Military Mefloquine Policy

by Remington L. Nevin

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Military policies that permit the continued use ofmefloquine expose militaries to certain unique risks not encountered with most civilian use of the drug. These risks, when fully recognized and acknowledged, exceed the drug's benefits in many military settings. While international drug regulators may consider a more limited set of risks when addressing issues in drug safety regulation, militaries must consider these additional risks in formulating policies for the rational use of this medication. Consideration of the issues in this review may aid militaries in formulating rational policies for the safer use of the drug. Depending on these militaries' risk tolerance, such consideration may serve to motivate further prohibitions on the use of mefloquine in line with those already in place in a growing number of military settings.

### Conflict of Interests

Remington L. Nevin has been retained as consultant and expert witness in legal cases involving claims of antimalarial drug toxicity.

### Authors' Contribution

Remington L. Nevin conceived the review and wrote the paper.

Travel Medicine and Infectious Disease • April 2015

# Eye disorders reported with the use of mefloquine (Lariam ) chemoprophylaxis: A drug safety database analysis

Miriam Adamcova a,*, Martin T. Schaerer a, Isabella Bercaru a,
Iain Cockburn a, Hans-Georg Rhein a, Patricia Schlagenhauf b

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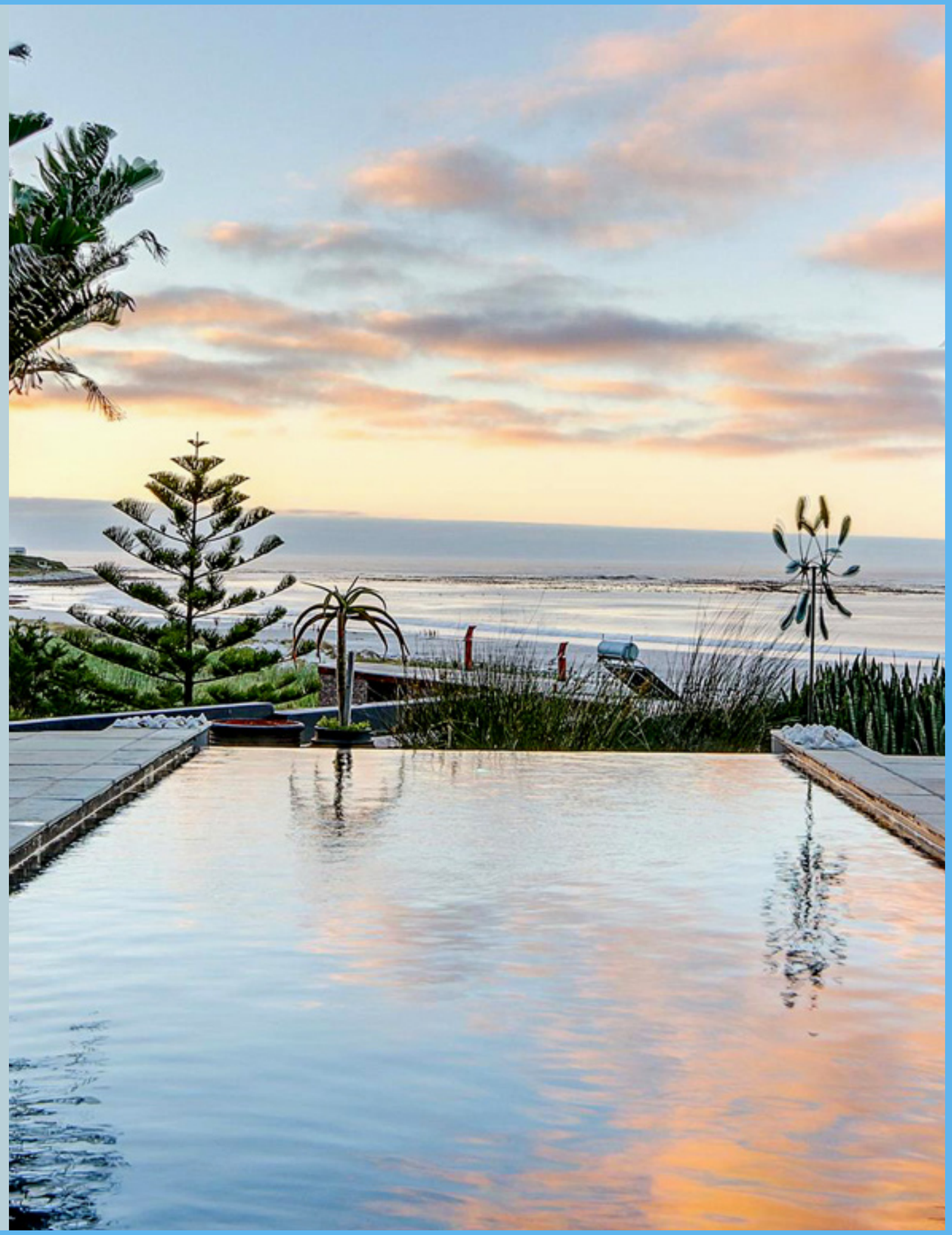
**Summary Background**: Between 80 and 90 million travellers visit malaria endemic areas annually and many require malaria chemoprophylaxis. The characterization of the risk and nature of eye disorders occurring during the use of malaria chemoprophylaxis is relevant for travel medicine advisors.
**Methods**: We did a database analysis on eye disorder adverse events reported for mefloquine (as Lariam ) using the F. Hoffmann-La Roche global drug safety database for the time frame February 1984 to January 18th, 2011. These adverse event reports were reviewed by a trained ophthalmologist. The analysis focused on 3 categories of eye disorders - Category 1: visual acuity; Category 2: anatomical parts of the eye and Category 3: neuro-ophthalmic events. To put our analysis in context, an extensive literature search on "mefloquine" and "eye disorders" was conducted.
**Results**: A total of 591 cases with 695 events assigned to the "Eye disorder" SOC in individuals exposed to mefloquine chemoprophylaxis were reported. The highest proportion of events (nZ493, 70.9%) was in Category 1: visual acuity (mainly visual impairment and blurred vision), followed by Category 3: neuro-ophthalmic events (n Z 124, 17.8%). The majority of visual adverse events were non-serious but 37.7% (n Z 223) of cases were classified as serious. Nine events of maculopathy were reported and 48 cases with 53 events described symptoms of optic neuropathy.
**Conclusions**: Mefloquine, like other anti-malarials, may be associated with eye disorders. Prescribers of anti-malarials should inform travellers regarding the risk of potential ocular side effects. Users of chemoprophylaxis who experience visual disorders should be referred to an ophthalmologist.



# Statement by Major Stuart McCarthy on Extensive Criminal Misconduct by Senior Australian Defence Force Officials

Posted on December 22, 2015 by International Mefloquine Veterans' Alliance

The Australian Defence Human Research Ethics Committee (ADHREC) minutes reported by The Sydney Morning Herald this morning provide further damning evidence of the extensive harm caused to Australian soldiers by the unethical drug trials conducted by the Army Malaria Institute (AMI) in Timor Leste in 2000-2002, and the ADF's 15-year long attempted cover-up. During my recent testimony to the Senate inquiry I called for a judicial inquiry into the conduct of the AMI, ADHREC and other parties. This evidence reinforces the need for an urgent judicial inquiry into what appears to be extensive criminal misconduct on the part of numerous senior ADF officials over many years. Such an inquiry should include a full audit of the records of every subject involved in the trials and their subsequent medical histories. The AMI and its contemptuous treatment of Australian soldiers as human guinea pigs is a dark stain on the hard-earned reputation of the Australian Army. Those soldiers, their families and the public now deserve to be told the truth, and the perpetrators of these crimes must now be held fully accountable before the law.

## AUSTRALIA, MAJOR McCARTHY AND MEFLOQUINE THE COVER-UP CONTINUES...

By IMVAlliance

The anti-malarial drug trial scandal that has embroiled the Australian Defence Force for the last two years simply won't go away, despite the government's best efforts to whitewash the controversy with a flawed "military justice" inquiry. There are growing calls for a public inquiry to investigate ethical breaches which occurred during a series of Army Malaria Institute (AMI) clinical trials conducted in Bougainville and Timor Leste from 1999 to 2002. The drugs in question are mefloquine, a neurotoxicant able to cause a "lasting or permanent" brain injury in a sizeable minority of users, and the experimental drug tafenoquine. The latter was found to be "more neurotoxic than mefloquine" by scientists from the US military research institute which developed both drugs. Tafenoquine was given to more than 1,500 ADF personnel during these trials, while mefloquine was used on 1,300 personnel. Mefloquine has probably been given to an additional 2,000 personnel since its introduction in the early 1990s. Hundreds of Australian veterans have since been diagnosed with serious neurological and psychiatric disorders, often mistaken for post-traumatic stress disorder. Many maintain they were compelled to participate in the trials. The Department of Veterans Affairs (DVA) has belatedly launched a health outreach program, admitting that the first cases "could be the tip of the iceberg". Media attention has to date focused on the health concerns of those affected and the ethical question of whether the subjects provided fully informed consent. Yet a deeper question is emerging,

***"At various times it was like living in a heavily armed lunatic asylum."***

namely a fundamental conflict between the commercial interests of the pharmaceutical industry and the public interests of the ADF. This could even result in criminal charges against ADF medical officials who conducted the trials and now hold senior military appointments. How could the ADF leadership have allowed this to happen?

Mefloquine and tafenoquine are both products of the US Walter Reed Army Institute of Research (WRAIR) anti-malarial drug discovery program which commenced during the Vietnam War. The results of early military tests of Mefloquine were given to the manufacturer Roche in one of the first public-private partnerships of its kind. These questionable results were then used to shortcut the approvals process by the US Food and Drug Administration (FDA) and other regulators. By the late 1990s Mefloquine was well known for its serious side effects and fell out of favour to the extent it is no longer manufactured by Roche in many countries. Linked to numerous war crimes, murders and suicides over the last 15 years, Mefloquine is now banned or regarded as a drug of last resort.

Tafenoquine is already repeating this tragic history, with the direct involvement of WRAIR and the closely affiliated AMI. The ADF's deployments to Bougainville and Timor Leste provided an ideal opportunity for AMI and WRAIR to conduct large-scale drug trials on a captive pool of "volunteers". Tafenoquine and Mefloquine were tested on almost every battalion of the Royal Australian Regiment. The results of several of these trials have not been published, presumably because they were unfavorable.

Of the reports that were published, none commented on the serious adverse effects that emerged from the trials. One report that was published found there was "no statistical difference" between tafenoquine and mefloquine in the rate of neurological and psychiatric side effects. Many of the subjects are to this day admitted to psychiatric hospitals or have subsequently suicided—yet the ADF has refused to conduct follow up health studies.

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A co-author of the published study has been stonewalling the proposed outreach program for years. Recently, he falsely informed doctors involved in the outreach program that there were "no recorded neuropsychiatric side effects" from tafenoquine; contrary to his original report which found one in eight of his subjects experienced such side effects. The results of this trial were re-analysed in a 2014 paperco-authored by the current Director of AMI to find that tafenoquine is 100% effective in preventing malaria. The lead author of this paper is a former WRAIR employee who now owns a niche pharmaceutical company awarded a contract by the US Army to develop the drug for registration with both the FDA and the Australian Therapeutic Goods Administration. Should the FDA approve, his company would be given a tradeable "priority review voucher" worth several hundred million dollars.

In the 1990s the Canadian government responded to a similar scandal involving an unlawful mefloquine drug trial on peacekeeping troops in Somalia by disbanding the regiment that was subjected to the experiment.

On the evidence already publicly available, a more appropriate response from the Australian government would be to disband AMI and prohibit the conduct of clinical drug trials on ADF personnel deployed on military operations. The ADF is clearly incapable of providing the corporate oversight needed to protect the interests of its troops against those of the pharmaceutical industry.

About 580 ADF members were prescribed mefloquine between 2000 and 2005. Another 1319 were prescribed as part of studies by the Army Malaria Institute in 2001 and 2002. About 25 ADF personnel are now treated with mefloquine each year.

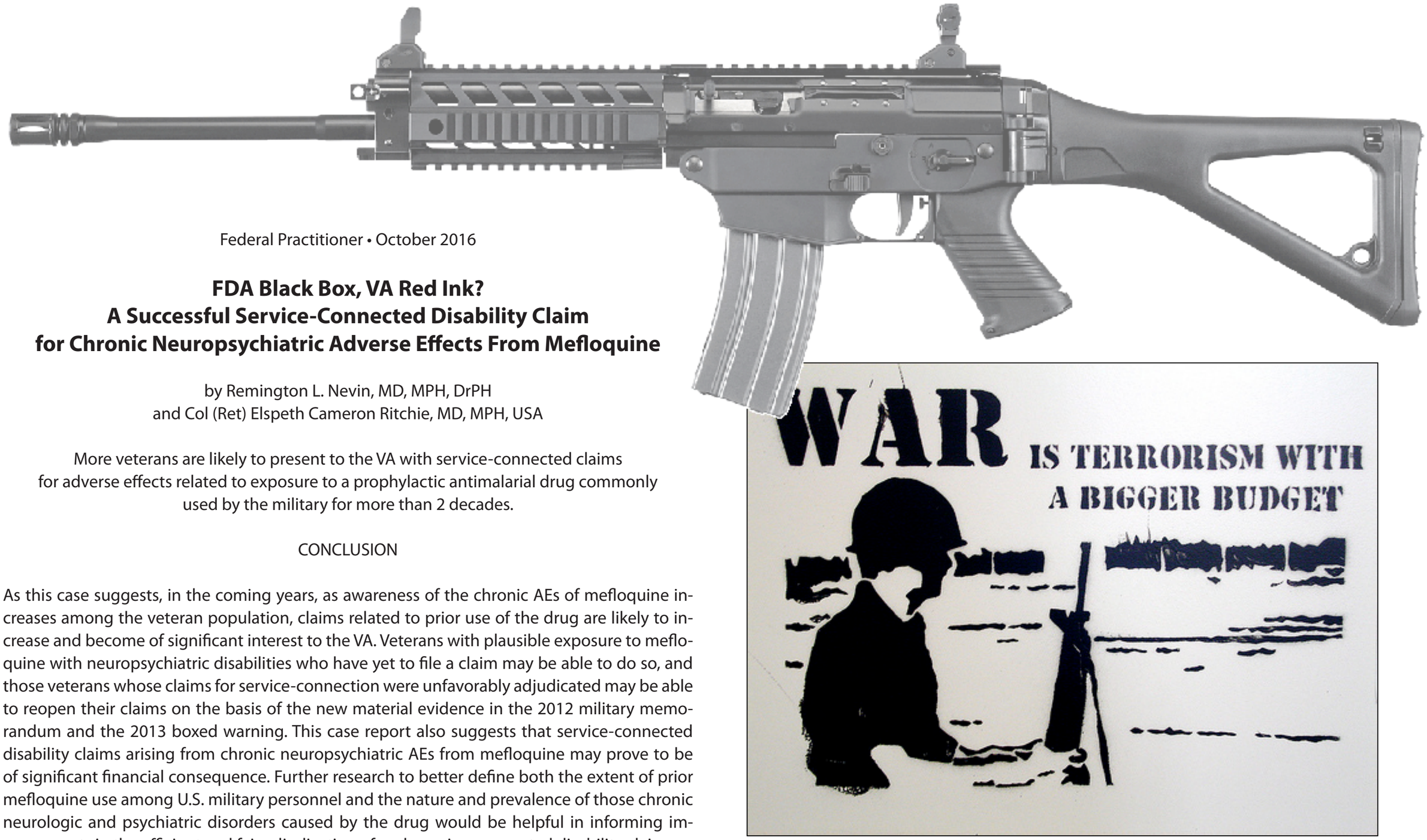
The trial also prescribed soldiers with the antimalarial tafenoquine despite it not being approved for use in Australia. The drug remains banned to this day.

Luke Grogan, who served with fourth battalion commandos in East Timor, said he became anxious and suffered vertigo after taking the drug during the trial period. He had trouble sleeping, would wake up screaming and punching the wall, and suffered blackouts. Mr Grogan was medically discharged from the army in 2011 but said a public inquiry would provide certainty his post-traumatic stress disorder was not exacerbated by the drug. Bill Harris, who served as an infantryman during the trial, said the drug had an immediate impact on him and many soldiers have remained silent about the side effects.

"I had nightmares that night and I woke up with a feeling of dread and anxiety," he said. "I had never felt like that before. For some time I kept my mouth shut about it because you were not allowed to serve in East Timor without an antimalarial.

Scott McCormick, who also served with the fourth battalion, said the group were told only one in 10,000 people would develop side effects and many favoured the drug as it was taken only weekly. "Mood swings and unusual behaviour were the norm on this deployment," he said.

"At various times it was like living in a heavily armed lunatic asylum. I myself developed sleep paralysis and generalised anxiety after the second or third dose, which then manifested into clinical depression."




Federal Practitioner • October 2016

# FDA Black Box, VA Red Ink? A Successful Service-Connected Disability Claim for Chronic Neuropsychiatric Adverse Effects From Mefloquine

by Remington L. Nevin, MD, MPH, DrPH
and Col (Ret) Elspeth Cameron Ritchie, MD, MPH, USA

More veterans are likely to present to the VA with service-connected claims for adverse effects related to exposure to a prophylactic antimalarial drug commonly used by the military for more than 2 decades.

## CONCLUSION

As this case suggests, in the coming years, as awareness of the chronic AEs of mefloquine increases among the veteran population, claims related to prior use of the drug are likely to increase and become of significant interest to the VA. Veterans with plausible exposure to mefloquine with neuropsychiatric disabilities who have yet to file a claim may be able to do so, and those veterans whose claims for service-connection were unfavorably adjudicated may be able to reopen their claims on the basis of the new material evidence in the 2012 military memorandum and the 2013 boxed warning. This case report also suggests that service-connected disability claims arising from chronic neuropsychiatric AEs from mefloquine may prove to be of significant financial consequence. Further research to better define both the extent of prior mefloquine use among U.S. military personnel and the nature and prevalence of those chronic neurologic and psychiatric disorders caused by the drug would be helpful in informing improvements in the efficient and fair adjudication of such service-connected disability claims.

***"These symptoms have been unresponsive to pharmacologic therapy and psychotherapy."***

Drug Safety Case Report • June 2016

## Prolonged Neuropsychiatric Symptoms in a Military Service Member Exposed to Mefloquine

by Jeffrey Livezey1, Thomas Oliver2 and Louis Cantilena2

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A 32-year-old male developed neuropsychiatric symptoms 2 weeks after starting mefloquine 250 mg/week for malaria prophylaxis. He continued to take the medication for the next 4 months. Initial symptoms included vivid dreams and anxiety, as well as balance problems. These symptoms persisted and progressed over the next 4 years to include vertigo, emotional lability, and poor short-term memory, which have greatly affected his personal and professional life. An extensive evaluation revealed objective evidence supporting a central vestibulopathy. These symptoms have been unresponsive to pharmacologic therapy and psychotherapy. A Naranjo assessment score of 6 was obtained for his initial symptoms, indicating a probable adverse drug reaction to mefloquine given the relationship between the clinical picture and drug exposure.

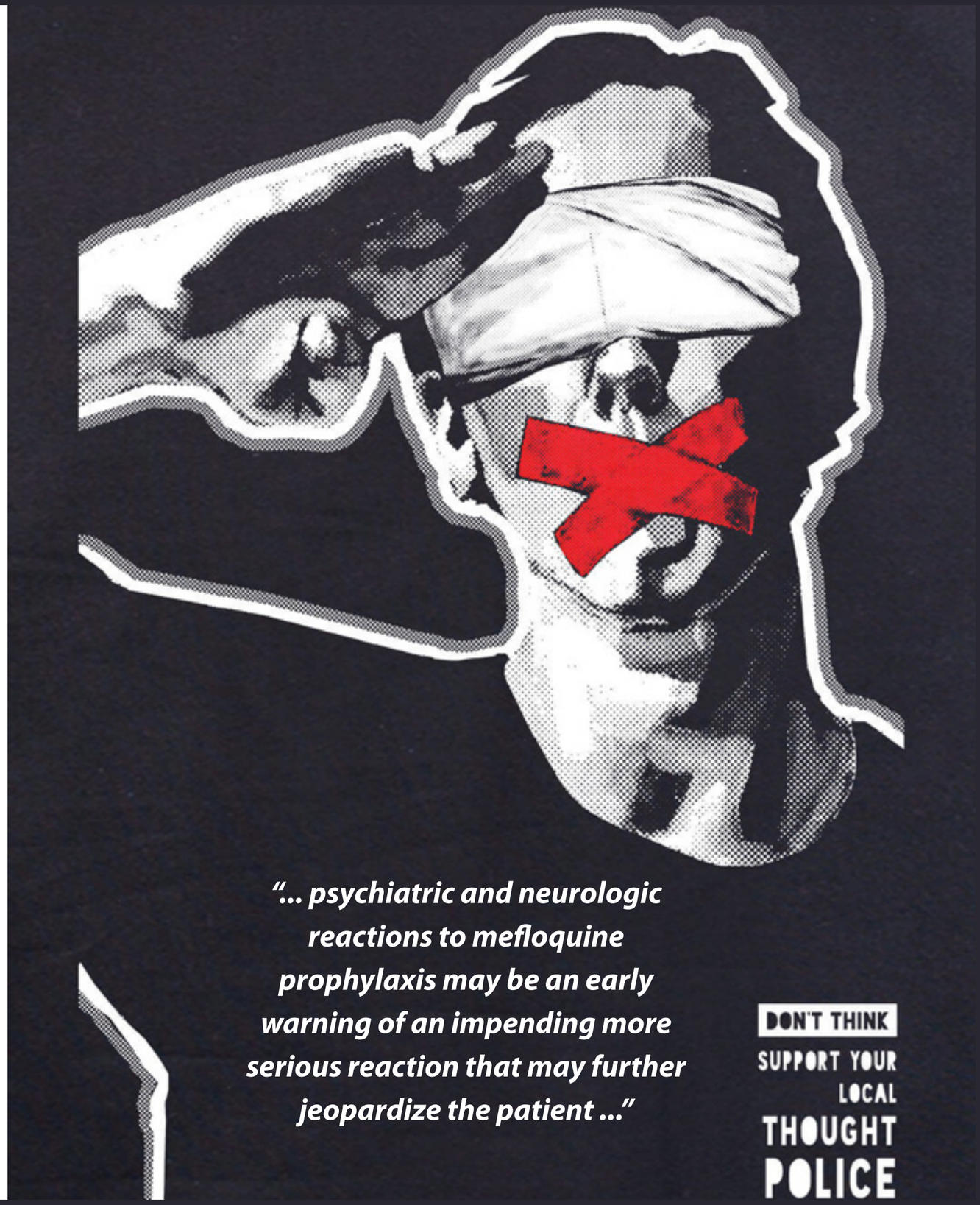
Pharmacology Research And Perspectives • 2017

# A serious nightmare: psychiatric and neurologic adverse reactions to mefloquine are serious adverse reactions

by Remington L. Nevin

Department of Environmental Health and Engineering
Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland

Mefloquine (originally marketed as Lariam) is a neurotoxic quinoline derivative antimalarial drug that is known to cause serious and potentially lasting neuropsychiatric adverse reactions. Since 2013, drug regulators in several jurisdictions, including the United States, the United Kingdom, Ireland, and Canada, have required their mefloquine labels be updated to warn that when used for malaria prophylaxis the drug should be discontinued at the onset of neurologic or psychiatric symptoms. These recent changes to the international labeling serve to imply that psychiatric and neurologic reactions to mefloquine prophylaxis may be an early warning of an impending more serious reaction that may further jeopardize the patient with continued use of the drug. To prevent these more serious effects, these drug labels now warn that mefloquine should be discontinued and that patients seek immediate medical intervention to obtain an alternative antimalarial drug when psychiatric or neurologic symptoms occur. When used correctly for malaria prophylaxis as the updated labeling now directs, it is reasonable to expect that mefloquine will be discontinued, and an alternative drug substituted, in each patient who develops psychiatric or neurologic symptoms. This opinion discusses the implications of this updated labeling for the reporting of adverse reactions and for the continued use of the drug in malaria prophylaxis.



American Journal of Tropical Medicine and Hygiene • 2017

Letter to the Editor

# Misclassification and Bias in Military Studies of Mefloquine

By Remington Lee Nevin
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Dear Sir:

I read with interest the recent analysis by Eick-Cost and others, which examined associations among U.S. military personnel between various neurologic and psychiatric diagnoses and earlier use of mefloquine.1 Although not accounting for multiple hypothesis testing, the authors' finding in subgroup analysis of a significantly increased risk of posttraumatic stress disorder (PTSD) with use of mefloquine is intriguing and calls for further investigation. The U.S. Food and Drug Administration has warned that neuropsychiatric adverse effects from mefloquine, unlike those from other antimalarials, may last years after use or even be permanent. These lasting effects, which may include vivid nightmares, disordered sleep, anxiety, irritability, anger, cognitive dysfunction, and dissociation, may mimic certain symptoms of PTSD.2 Recently, several cases have been reported in which these symptoms have been misattributed among U.S. military personnel to PTSD.2,3 Potentially consistent with such adverse effects from mefloquine being more broadly misattributed to PTSD, among a nondeployed subgroup the Eick-Cost analysis found a nearly doubled risk of the diagnosis among those prescribed mefloquine as compared with those prescribed atovaquone-proguanil, after adjusting for common confounders. Although a significant association of PTSD diagnosis with mefloquine was not seen in comparison to doxycycline, this may reflect the effects of differential exposure misclassification and selection bias. Many of the subjects in the doxycycline cohort were deployed to combat in Afghanistan, during a time when policy changes beginning in 2009 made doxycycline the preferred antimalarial,4 and when drug use was

increasingly subject to electronic documentation. In contrast, for much of the prior two decades when mefloquine had been the drug of choice for combat deployments, its use was often undocumented.2,5 As many of the subjects in the doxycycline cohort may be expected to have had one or more prior combat deployments, they may also have had prior undocumented exposure to mefloquine. Any lasting effects from such exposure may consequently have been misclassified in the Eick-Cost analysis as being due to doxycycline rather than to mefloquine. Furthermore, the presence of such lasting effects, even if not resulting in a diagnosis but only a prescription of a psychotropic medication to control symptoms, may have made subsequent exposure to mefloquine less likely, as a prior study has shown.6 Both this misclassification and bias may have had the effect of decreasing subsequent neurologic and psychiatric diagnoses in the mefloquine cohort relative to the doxycycline cohort, diluting any observed associations. These limitations may potentially be overcome by restricting future investigations to military personnel without prior deployments and without evidence of prior neuropsychiatric contraindications to mefloquine use.7 A previous underpowered analysis of U.S. military hospitalizations found a trend toward increased risk with mefloquine of diagnosis of vertigo and adjustment disorder,8 a condition which often precedes PTSD. These trends are generally mirrored in the Eick-Cost subgroup analysis. Future investigations should consider a revised outcome of interest defined by informed combinations of these and related neurologic and psychiatric diagnoses. A combination of such diagnoses may be more specific than single diagnoses in retrospectively identifying the characteristic syndrome of lasting neuropsychiatric adverse effects caused by the drug.

FDA Drug Safety Communication:

# FDA approves label changes for antimalarial drug mefloquine hydrochloride due to risk of serious psychiatric and nerve side effects

[7-29-2013] The U.S. Food and Drug Administration (FDA) is advising the public about strengthened and updated warnings regarding neurologic and psychiatric side effects associated with the antimalarial drug mefloquine hydrochloride. A boxed warning, the most serious kind of warning about these potential problems, has been added to the drug label. FDA has revised the patient Medication Guide dispensed with each prescription and wallet card to include this information and the possibility that the neurologic side effects may persist or become permanent. The neurologic side effects can include dizziness, loss of balance, or ringing in the ears. The psychiatric side effects can include feeling anxious, mistrustful, depressed, or having hallucinations (For a more complete list of potential side effects, see Additional Information for Patients).

Neurologic side effects can occur at any time during drug use, and can last for months to years after the drug is stopped or can be permanent. Patients, caregivers, and health care professionals should watch for these side effects. When using the drug to prevent malaria, if a patient develops neurologic or psychiatric symptoms, mefloquine should be stopped, and an alternate medicine should be used. If a patient develops neurologic or psychiatric symptoms while on mefloquine, the patient should contact the prescribing health care professional. The patient should not stop taking mefloquine before discussing symptoms with the health care professional.

Malaria is a serious disease caused by a parasite that commonly infects mosquitoes, which then bite humans. It is a major cause of death worldwide but is less common in the United States. The disease is a problem primarily in developing countries with warm climates. Persons who travel to these countries may be at risk of malaria infection and should take drugs to prevent or reduce that risk. People with malaria often experience fever, chills, and flu-like symptoms. Drugs must be taken to treat the disease if you have been infected, but may, themselves, have side effects. FDA will continue to evaluate the safety of mefloquine and will communicate with the public again if additional information becomes available.

## FACTS about mefloquine tablets

• Antimalarial drug indicated for the treatment of mild to moderate acute malaria caused by mefloquine-susceptible P. falciparum and P. vivax.
• Also indicated for the prevention of malaria infections by P. falciparum (including chloroquine-resistant P. falciparum) and P. vivax.
• Previously marketed under the brand name Lariam; however, the Lariam product is not currently marketed. Generic mefloquine products are available in the US.

## Additional Information for Patients

• Mefloquine may cause dizziness, balance problems, and ringing in the ears. These symptoms can occur at any time during use and can last for months to years after the drug is stopped or can be permanent.

• Contact your health care professional right away if you take mefloquine and experience any of the following signs and symptoms; it may be necessary to stop mefloquine and take another medication to prevent malaria, but do not do so without first talking with your health care professional:

o Dizziness
o Balance problems such as a feeling that you or things around you are moving or spinning (vertigo)
o Ringing in your ears (tinnitus)
o Convulsions or seizures
o Inability to sleep (insomnia)

• If you already have or develop any mental problems, you should contact your health care professional right away. These mental problems include:

o Anxiety
o Feelings of mistrust towards others (paranoia)
o Seeing or hearing things that are not there (hallucinations)
o Depression
o Restlessness
o Confusion
o Behavior that is unusual

• Carefully read the Medication Guide and the wallet card that come with your mefloquine prescription.
• Discuss any questions or concerns about mefloquine with your health care professional
• Report any side effects you experience to your health care professional and the FDA MedWatch program, using the information in the Contact FDA box at the bottom of the page.

Additional Information for Health Care Professionals

- Encourage your patients to contact you if they develop neurologic or psychiatric symptoms.
- Make sure your patients receive the Medication Guide with every prescription.
- Be alert to the potential for the development of neurologic and psychiatric adverse reactions in patients using the drug. If the patient develops psychiatric or neurologic symptoms during preventive use, mefloquine should be stopped and an alternate antimalarial medicine should be used.
- Neurologic and psychiatric symptoms can be difficult to identify in children.
- Report adverse reactions involving mefloquine to the FDA MedWatch program, using the information in the Contact FDA box at the bottom of the page.

## Data Summary

The mefloquine drug label already states that mefloquine should not be prescribed to prevent malaria in patients with major psychiatric disorders or with a history of seizures. The changes to the mefloquine drug label better describe the possibility of persistent neurologic (vestibular) adverse effects after mefloquine is discontinued and the possibility of permanent vestibular damage.

In conducting its assessment of vestibular adverse reactions associated with mefloquine use, FDA reviewed adverse event reports from the FDA Adverse Event Reporting System (FAERS) and the published literature, identifying patients that reported one or more vestibular symptoms such as dizziness, loss of balance, tinnitus, and vertigo. Patients who reported vestibular adverse reactions were healthy with no known major medical problems prior to taking mefloquine for malaria prophylaxis. Some patients did not suspect their symptoms were due to mefloquine and continued to take the drug after the symptoms started.

In many cases, these symptoms developed early in the course of treatment, sometimes after one or two doses of mefloquine. Dizziness, loss of balance, tinnitus, or vertigo persisted for months to years after mefloquine was discontinued, and permanent vestibular damage was diagnosed in some cases. These symptoms interfered with patients' daily activities and ability to work. Some cases described abnormal vestibular function tests and a diagnosis of vestibular damage. In some cases, the vestibular damage was thought to be caused by mefloquine use. Some patients reported recurrence of psychiatric and vestibular symptoms when they took mefloquine for the second time. Patients who experienced vestibular symptoms usually had concomitant psychiatric symptoms such as anxiety, confusion, paranoia, and depression. Some of the psychiatric symptoms persisted for months to years after mefloquine was discontinued.

FDA will continue to evaluate the safety of mefloquine and will communicate again if additional information becomes available.

# Guidelines for Treatment of Malaria in the United States

**(Based on drugs currently available for use in the United States – updated July 1, 2013)**

**CDC Malaria Hotline: (770) 488-7788 or (855) 856-4713 toll-free Monday-Friday 9 am to 5 pm EST - (770) 488-7100 after hours, weekends and holidays**

| Clinical Diagnosis/ *Plasmodium* species | Region Infection Acquired | Recommended Drug and Adult Dose[1] | Recommended Drug and Pediatric Dose[1] *Pediatric dose should NEVER exceed adult dose* |
|---|---|---|---|
| **Uncomplicated malaria/** *P. falciparum* or Species not identified<br><br>If "species not identified" is subsequently diagnosed as *P. vivax* or *P ovale:* see *P. vivax* and *P ovale* (below) re. treatment with primaquine | **Chloroquine-resistant or unknown resistance[2]**<br>(All malarious regions except those specified as chloroquine-sensitive listed in the box below.) | **A. Atovaquone-proguanil (Malarone™)[3]**<br>**Adult tab = 250 mg atovaquone/ 100 mg proguanil**<br>4 adult tabs po qd x 3 days | **A. Atovaquone-proguanil (Malarone™)[3]**<br>**Adult tab = 250 mg atovaquone/ 100 mg proguanil**<br>**Peds tab = 62.5 mg atovaquone/ 25 mg proguanil**<br>5 - 8kg: 2 peds tabs po qd x 3 d<br>9-10kg: 3 peds tabs po qd x 3 d<br>11-20kg: 1adult tab po qd x 3 d<br>21-30kg: 2 adult tabs po qd x 3d<br>31-40kg: 3 adult tabs po qd x 3d<br>> 40 kg: 4 adult tabs po qd x 3d |
| | | **B. Artemether-lumefantrine (Coartem™)[3]**<br>**1 tablet = 20mg artemether and 120 mg lumefantrine**<br>A 3-day treatment schedule with a total of 6 oral doses is recommended for both adult and pediatric patients based on weight. The patient should receive the initial dose, followed by the second dose 8 hours later, then 1 dose po bid for the following 2 days.<br>5 - <15 kg: 1 tablet per dose<br>15 - <25 kg: 2 tablets per dose<br>25 - <35 kg: 3 tablets per dose<br>≥35 kg: 4 tablets per dose | |
| | | **C. Quinine sulfate plus one of the following: Doxycycline, Tetracycline, or Clindamycin**<br>**Quinine sulfate:** 542 mg base (=650 mg salt)[4] po tid x 3 or 7 days[5]<br>**Doxycycline:** 100 mg po bid x 7 days<br>**Tetracycline:** 250 mg po qid x 7 days<br>**Clindamycin:** 20 mg base/kg/day po divided tid x 7 days | **C. Quinine sulfate[4] plus one of the following: Doxycycline[6], Tetracycline[6] or Clindamycin**<br>**Quinine sulfate:** 8.3 mg base/kg (=10 mg salt/kg) po tid x 3 or 7 days[5]<br>**Doxycycline:** 2.2 mg/kg po every 12 hours x 7 days<br>**Tetracycline:** 25 mg/kg/day po divided qid x 7 days<br>**Clindamycin:** 20 mg base/kg/day po divided tid x 7 days |
| | | **D. Mefloquine (Lariam™ and generics)[7]**<br>684 mg base (=750 mg salt) po as initial dose, followed by 456 mg base (=500 mg salt) po given 6-12 hours after initial dose<br>Total dose= 1,250 mg salt | **D. Mefloquine (Lariam™ and generics)[7]**<br>13.7 mg base/kg (=15 mg salt/kg) po as initial dose, followed by 9.1 mg base/kg (=10 mg salt/kg) po given 6-12 hours after initial dose. Total dose= 25 mg salt/kg |

[1] If a person develops malaria despite taking chemoprophylaxis, that particular medicine should not be used as a part of their treatment regimen. Use one of the other options instead.

[2] NOTE: There are 4 options (A, B, C, or D) available for treatment of uncomplicated malaria caused by chloroquine-resistant *P. falciparum*. Options A, B, and C are equally recommended. Because of a higher rate of severe neuropsychiatric reactions seen at treatment doses, we do not recommend option D (mefloquine) unless the other options cannot be used. For option C, because there is more data on the efficacy of quinine in combination with doxycycline or tetracycline, these treatment combinations are generally preferred to quinine in combination with clindamycin.

[3] Take with with food or whole milk. If patient vomits within 30 minutes of taking a dose, then they should repeat the dose.

[4] US manufactured quinine sulfate capsule is in a 324mg dosage; therefore 2 capsules should be sufficient for adult dosing. Pediatric dosing may be difficult due to unavailability of non-capsule forms of quinine.

[5] For infections acquired in Southeast Asia, quinine treatment should continue for 7 days. For infections acquired elsewhere, quinine treatment should continue for 3 days.

[6] Doxycycline and tetracycline are not indicated for use in children less than 8 years old. For children less than 8 years old with chloroquine-resistant *P. falciparum*, atovaquone-proguanil and artemether-lumefantrine are recommended treatment options; mefloquine can be considered if no other options are available. For children less than 8 years old with chloroquine-resistant *P. vivax*, mefloquine is the recommended treatment. If it is not available or is not being tolerated and if the treatment benefits outweigh the risks, atovaquone-proguanil or artemether-lumefantrine should be used instead.

[7] Treatment with mefloquine is not recommended in persons who have acquired infections from Southeast Asia due to drug resistance.

[8] When treating chloroquine-sensitive infections, chloroquine and hydroxychloroquine are recommended options. However, regimens used to treat chloroquine-resistant infections may also be used if available, more convenient, or preferred.

[9] Primaquine is used to eradicate any hypnozoites that may remain dormant in the liver, and thus prevent relapses, in *P. vivax* and *P. ovale* infections. Because primaquine can cause hemolytic anemia in G6PD-deficient persons, G6PD screening must occur prior to starting treatment with primaquine. For persons with borderline G6PD deficiency or as an alternate to the above regimen, primaquine may be given 45 mg orally one time per week for 8 weeks; consultation with an expert in infectious disease and/or tropical medicine is advised if this alternative regimen is considered in G6PD-deficient persons. Primaquine must not be used during pregnancy.

# Guidelines for Treatment of Malaria in the United States

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| | | | |
|---|---|---|---|
| **Uncomplicated malaria/** *P. falciparum* or *Species not identified* | **Chloroquine-sensitive** (Central America west of Panama Canal; Haiti; the Dominican Republic; and most of the Middle East) | **Chloroquine phosphate (Aralen™ and generics)**[8]<br>600 mg base (=1,000 mg salt) po immediately, followed by 300 mg base (=500 mg salt) po at 6, 24, and 48 hours<br>Total dose: 1,500 mg base (=2,500 mg salt) **OR**<br>**Hydroxychloroquine (Plaquenil™ and generics)**<br>620 mg base (=800 mg salt) po immediately, followed by 310 mg base (=400 mg salt) po at 6, 24, and 48 hours<br>Total dose: 1,550 mg base (=2,000 mg salt) | **Chloroquine phosphate (Aralen™ and generics)**[8]<br>10 mg base/kg po immediately, followed by 5 mg base/kg po at 6, 24, and 48 hours<br>Total dose: 25 mg base/kg **OR**<br>**Hydroxychloroquine (Plaquenil™ and generics)**<br>10 mg base/kg po immediately, followed by 5 mg base/kg po at 6, 24, and 48 hours<br>Total dose: 25 mg base/kg |
| **Uncomplicated malaria/** *P. malariae or P. knowlesi* | **All regions** | **Chloroquine phosphate:**[8] Treatment as above **OR**<br>**Hydroxychloroquine:** Treatment as above | **Chloroquine phosphate:**[8] Treatment as above **OR**<br>**Hydroxychloroquine:** Treatment as above |
| **Uncomplicated malaria/** *P. vivax* or *P. ovale* | **All regions**<br>Note: for suspected chloroquine-resistant *P. vivax*, see row below | **Chloroquine phosphate**[8] **plus Primaquine phosphate**[9]<br>**Chloroquine phosphate:** Treatment as above<br>**Primaquine phosphate:** 30 mg base po qd x 14 days **OR**<br>**Hydroxychloroquine plus Primaquine phosphate**[9]<br>**Hydroxychloroquine:** Treatment as above<br>**Primaquine phosphate:** 30 mg base po qd x 14 days | **Chloroquine phosphate**[8] **plus Primaquine phosphate**[9]<br>**Chloroquine phosphate:** Treatment as above<br>**Primaquine:** 0.5mg base/kg po qd x 14 days **OR**<br>**Hydroxychloroquine plus Primaquine phosphate**[9]<br>**Hydroxychloroquine:** Treatment as above<br>**Primaquine phosphate:** 0.5mg base/kg po qd x 14 days |
| **Uncomplicated malaria/** *P. vivax* | **Chloroquine-resistant**[10] (Papua New Guinea and Indonesia) | **A. Quinine sulfate plus either Doxycycline or Tetracycline plus Primaquine phosphate**[9]<br>**Quinine sulfate:** Treatment as above<br>**Doxycycline or Tetracycline:** Treatment as above<br>**Primaquine phosphate:** Treatment as above | **A. Quinine sulfate plus either Doxycycline**[6] **or Tetracycline**[6] **plus Primaquine phosphate**[9]<br>**Quinine sulfate:** Treatment as above<br>**Doxycycline or Tetracycline:** Treatment as above<br>**Primaquine phosphate:** Treatment as above |
| | | **B. Atovaquone-proguanil plus Primaquine phosphate**[9]<br>**Atovaquone-proguanil:** Treatment as above<br>**Primaquine phosphate:** Treatment as above | **B. Atovaquone-proguanil plus Primaquine phosphate**[9]<br>**Atovaquone-proguanil:** Treatment as above<br>**Primaquine phosphate:** Treatment as above |
| | | **C. Mefloquine plus Primaquine phosphate**[9]<br>**Mefloquine:** Treatment as above<br>**Primaquine phosphate:** Treatment as above | **C. Mefloquine plus Primaquine phosphate**[9]<br>**Mefloquine:** Treatment as above<br>**Primaquine phosphate:** Treatment as above |
| **Uncomplicated malaria: alternatives for pregnant women**[11,12,13] | **Chloroquine-sensitive** (see uncomplicated malaria sections above for chloroquine-sensitive species by region) | **Chloroquine phosphate:** Treatment as above **OR**<br>**Hydroxychloroquine:** Treatment as above | Not applicable |
| | **Chloroquine-resistant** (see sections above for regions with chloroquine resistant *P. falciparum and P. vivax*) | **Quinine sulfate plus Clindamycin**<br>**Quinine sulfate:** Treatment as above<br>**Clindamycin:** Treatment as above<br>**OR**<br>**Mefloquine:** Treatment as above | Not applicable |

[10] NOTE: There are three options (A, B, or C) available for treatment of uncomplicated malaria caused by chloroquine-resistant *P. vivax*. High treatment failure rates due to chloroquine-resistant *P. vivax* have been well documented in Papua New Guinea and Indonesia. Rare case reports of chloroquine-resistant *P. vivax* have also been documented in Burma (Myanmar), India, and Central and South America. Persons acquiring *P. vivax* infections outside of Papua New Guinea or Indonesia should be started on chloroquine. If the patient does not respond, the treatment should be changed to a chloroquine-resistant *P. vivax* regimen and CDC should be notified (Malaria Hotline number listed above). For treatment of chloroquine-resistant *P. vivax* infections, options A, B, and C are equally recommended.

[11] For pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant *P. falciparum* or chloroquine-resistant *P. vivax* infection, treatment with doxycycline or tetracycline is generally not indicated. However, doxycycline or tetracycline may be used in combination with quinine (as recommended for non-pregnant adults) if other treatment options are not available or are not being tolerated, and the benefit is judged to outweigh the risks.

[12] Atovaquone-proguanil and artemether-lumefantrine are generally not recommended for use in pregnant women, particularly in the first trimester due to lack of sufficient safety data. For pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant *P. falciparum* infection, atovaquone-proguanil or artemether-lumefantrine may be used if other treatment options are not available or are not being tolerated, and if the potential benefit is judged to outweigh the potential risks.

[13] For *P. vivax* and *P. ovale* infections, primaquine phosphate for radical treatment of hypnozoites should not be given during pregnancy. Pregnant patients with *P. vivax* and *P. ovale* infections should be maintained on chloroquine prophylaxis for the duration of their pregnancy. The chemoprophylactic dose of chloroquine phosphate is 300 mg base (=500 mg salt) orally once per week. After delivery, pregnant patients who do not have G6PD deficiency should be treated with primaquine.

Hello
my name is
Grief
Hello
my name is
Anxiety
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Phobia
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POST-TRAUMATIC
STRESS
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STRESS
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Shame
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DEPRESSION
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PANIC

*LARIAM also known as MEFLOQUINE for Malaria Prophylaxis*

*Talk To People About It*